Bleeding Syndromes

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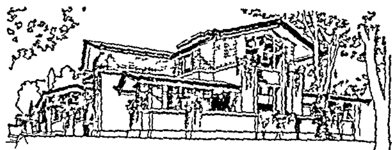
BLEEDING SYNDROMES

A CLINICAL MANUAL

By

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TO
MARIAN
and
BILL AND MARTHA

FOREWORD

THIS book is a compilation of practical information about the clinical picture pathogenesis diagnosis and treatment of hemorrhagic diseases, written for the practicing physician It is not intended as a laboratory manual for the differentiation of bleeding disorders nor as a review of the current literature on the physiology of hemostasis An extensive bibliography restricted whenever possible to readily available journals will lead the interested reader to more detailed and often more abstruse information and opinion Like any other this monograph reflects the accumulated prejudices of the writer My views have been influenced by the individuals with whom I have studied and worked—Arthur J Patek Jr George S Mirick C Lockard Conley T Hale Ham Jack A Pritchard Alvin Margolius Jr and the late Louis Pillemer—and the many Cleveland physician friends who have shared their clinical experiences with me Otherwise unpublished laboratory studies were supported by grants from the National Heart Institute of the National Institutes of Health the Cleveland Area Heart Society the American Heart Association and the Cleveland Chapter of the Arthritis and Rheumatism Foundation The laboratory studies could not have been done without the able assistance of Mrs Rosemary Ashe Mrs Velma Axelrod Miss Joan Colopy Miss Sedell Millman Miss Ann Harris and Mrs Barbara Sayles The bulk of the labor in arranging and typing the manuscript was Miss June Patton s Mention must also be made of a by product of my efforts I have learned why so many authors dedicate their writings to their wives They deserve it

O D R

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Bleeding Syndromes

Chapter I

THE PHYSIOLOGY OF HEMOSTASIS

ALL but the simplest forms of life require the maintenance of an intravascular circulation Numerous devices have evolved to protect the organism against loss of the circulating fluid In mammals at least four such mechanisms are available The blood which escapes through an injured vascular wall may form a gelatinous coagulum which plugs the defect stopping further bleeding If the injury is small enough platelets may pile up at the site of injury sealing the wound The flow of blood to a damaged area may also be decreased by constriction of the afferent vessels Finally, the blood vessels within a muscular organ may be compressed by the contraction of extravascular tissues Excessive blood loss may result from failure of any of these devices

BLOOD CLOTTING MECHANISMS

In the process of clotting fluid blood is transformed into a solid mass In the seventeenth century Malpighi demonstrated that this mass contained a white fibrous substance separable from the red blood corpuscles How this substance solid *fibrin* forms during clotting has been studied intensively for almost two centuries Fibrin is a tough fibrous protein arranged in a network of interlacing strands in whose interstices the blood cells are entrapped It is apparently a polymer composed of needle like units of a protein of high molecular weight Normally these units do not exist as such in the circulating blood but form during coagulation from a soluble precursor *fibrinogen* Fibrinogen too is a long narrow protein of high molecular weight (597), synthesized only in the presence of functioning liver tissue

The conversion of soluble fibrinogen into insoluble fibrin takes

place through the action of *thrombin* which evolves during the clotting process The enzymatic nature of this reaction, long suspected has been demonstrated by two independent methods Bettleheim and Bailey (62) and Lorand and Middlebrook (376) showed that thrombin was proteolytic, splitting small polypeptide chains from the ends of each fibrinogen molecule Moreover, Sherry and Troll (593) found that thrombin like trypsin and some other proteolytic enzymes hydrolyzed certain synthetic esters of amino acids notably para toluenesulfonylarginine methyl ester These observations intimate that the ultimate step in the coagulation of blood is the hydrolysis of fibrinogen to form molecules of soluble fibrin which then polymerize into macroscopic fibrin strands

Thrombin can react with fibrinogen in the absence of calcium ions However, *calcium* in the concentration present in normal plasma greatly accelerates the reaction (584) and increases the strength of the fibers (206), indicating that under physiologic conditions this ion is important in the formation of fibrin The conversion of fibrinogen to fibrin is also accelerated by a protein component of plasma (532) perhaps identified with the albumin fraction (312) Whether this fraction contains a specific clotting factor or accelerates clotting because of its non specific colloidal nature is not clear Either this, or more probably another plasma protein must be present for calcium to exert its clot toughening effect (596 375)

TABLE I

GLOSSARY OF CLOTTING TERMS *

Fibrinogen Profibrin Factor I

Thrombin Thrombase Fibrin Ferment Biothrombin

Prothrombin Prothrombase Thrombogen Prothrombin B Component A Factor II

Thromboplastin Thrombokinase (Some authors make a distinction between thromboplastin and thrombokinase) Factor III

Calcium Factor IV

Accelerin Activated Factor V Factor VI Serum Accelerator Globulin, Serum Ac-globulin Serum Accelerator Prothrombinase

* Modified from (534) with the kind permission of the Year Book Publishers Chicago

TABLE I (Continued)

Proaccelerin. Factor V Labile Factor Plasma Accelerator Globulin, Plasma Ac-globulin, Prothrombin Accelerator Plasmatic Co-Factor of Thromboplastin, Prothrombin A Thrombogene Plasma Prothrombin Conversion Factor Proprothrombinase

Serum Factors Needed for the Conversion of Prothrombin to Thrombin
Prior to 1956 the factors in serum accelerating the conversion of prothrombin to thrombin by thromboplastin were referred to collectively by many names What was assumed to be the active agent was called Convertin, Serum Prothrombin Conversion Accelerator (SPCA) Activated Thromboplastin, Stable Factor but different authors understood these terms differently
The inactive precursor was called Proconvertin, Co-Thromboplastin, Precursor of Serum Prothrombin Conversion Accelerator (Pro-SPCA) Prothrombin Conversion Factor Prothrombin Accelerator Co-Factor V Serum Accelerator Factors VII and X, Kappa Factor Autoprothrombin I Serozyme.
More recent studies suggests that these factors are multiple Two groups have been differentiated

Pro-SPCA Factor VII Co-Thromboplastin
Stuart Factor Factor X, Prower Factor

Antihemophilic Factor Antihemophilic Globulin, Globulin Substance, Plasma Thromboplastic Factor Antihemophilic Factor A Antihemophilic Globulin A, Plasmokinin, Thrombocatalysin Thrombocytolysin, Platelet Co-Factor I Thromboplastic Plasma Component Factor VIII Plasma Thromboplastic Factor A, Prothrombokinase Thromboplastinogen

Christmas Factor Plasma Thromboplastin Component (PTC) Factor IX, Platelet Co-Factor II Antihemophilic Factor B Plasma Thromboplastic Factor B Autoprothrombin II Beta Prothromboplastin

Plasma Thromboplastin Antecedent PTA Plasma Thromboplastic Factor C Factor XI Antihemophilic Factor C

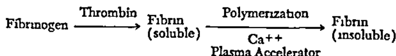
Hageman Factor Clot Promoting Factor Fifth Plasma Thromboplastin Precursor Antihemophilic Factor D

Plasmin. Fibrinolysin Tryptase, Lysin, Serum Trypsin, Plasma Proteolytic Enzyme

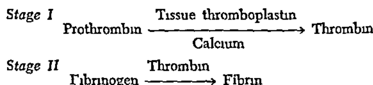
Plasminogen Proplasmin, Profibrinolysin Serum Tryptogen

Platelets Thrombocytes

The last stages of the clotting process can be summarized as follows



As one would anticipate, thrombin does not exist in any appreciable concentration in the circulating blood for if it did the available fibrinogen would clot immediately Instead thrombin is present in the form of a precursor *prothrombin,* a protein synthesized, probably in the liver (610), only in the presence of Vitamin K (511) Vitamin K is provided almost entirely by the bacterial flora of the intestinal tract, from which it is absorbed with the aid of bile salts How prothrombin is converted to thrombin, a molecule of about half its molecular weight, is unsolved In the latter part of the nineteenth century Schmidt demonstrated that clotting can be initiated by the adding of particles of tissue to plasma. He believed that these tissue particles or *thromboplastin* convert prothrombin to thrombin and this in turn clots fibrinogen At about the same time Hammersten demonstrated that *calcium* is needed for the formation of thrombin from prothrombin These ideas were combined by Morawitz (445) into a now classic theory of blood coagulation



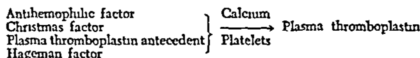
The way in which thromboplastin alters the prothrombin molecule remains unexplained

It was soon found that blood drawn with great care to avoid the admixture of tissue nonetheless clots rapidly when placed in glass tubes At first it was assumed that the blood cells are so altered when they are removed from the body that they furnish thromboplastin analagous to that of other tissues Platelets red blood cells and white blood cells have each been implicated as a source of thromboplastin in shed blood However at the turn of the century Bordet and Gengou (86) demonstrated that plasma separated from blood cells by prolonged centrifugation clots readily in glass tubes This observation, repeatedly confirmed by progressively finer techniques, implies that the plasma itself may provide "thromboplastic" activity when blood is shed

A number of different factors have been described which seem

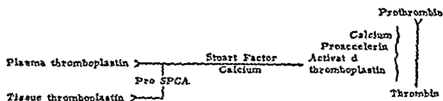
to be required for the development of thromboplastic activity in plasma These include *antihemophilic factor* (479), *Christmas factor* or plasma thromboplastin component (576, 70), *plasma thromboplastin antecedent* (568) and *Hageman factor* (537) The properties of these factors will be discussed in subsequent chapters

The optimal formation of thromboplastin in shed blood also requires the presence of calcium ions and of platelets (69) Crude "cephalin" mixtures (52), rich in the phospholipids phosphatidyl serine and phosphatidyl ethanolamine can apparently substitute for platelets at this step How these various factors interreact is not yet clear One may assume that when blood is shed a succession of reactions is initiated producing an agent functionally similar to tissue thromboplastin These reactions may be summarized in this way



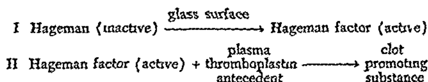
Were this not complicated enough at least three additional factors are needed for the interaction between thromboplastin and prothrombin namely *pro-SPCA* (24) *Stuart factor* (292 656) and *proaccelerin* (475) Pro-SPCA (that is the precursor of serum prothrombin conversion accelerator) and Stuart factor are relatively stable substances remarkably similar in their characteristics found both in normal plasma and serum Separated from each other only recently they were formerly known collectively as *proconvertin* or *stable factor*/Stuart factor is required for the optimal action of thromboplastin originating either from the plasma or tissues while pro SPCA may be needed only for the action of tissue thromboplastin These factors as well as prothrombin and Christmas factor require Vitamin K for their synthesis Proaccelerin an unstable protein found in normal plasma but not in human serum is probably inactive in the circulating plasma changing during clotting to an active substance *accelerin* perhaps by the action of thrombin/Accelerin greatly accelerates the conversion of prothrombin to thrombin by throm

boplastin, pro-SPCA and Stuart factor. Little is known about the mode of action of the pro SPCA Stuart factor and proaccelerin, nor indeed, of the order in which they act, probably a product of the interaction between thromboplastin, pro SPCA and Stuart factor reacts in turn with accelerin A tentative hypothesis can be represented in this manner



This formulation suggests that pro SPCA and Stuart factor alter thromboplastin which then converts prothrombin to thrombin The converse hypothesis is equally supportable, that is that thromboplastin changes pro SPCA and Stuart factor into active substances which convert prothrombin to thrombin

The forces which maintain blood in a liquid state within the vessels but induce clotting when blood is shed are essentially unknown. The first step in coagulation appears to be the activation of Hageman factor (589 411, 546) This substance seems to be inert in the circulating blood, but becomes active when exposed to glass or certain adsorbents Next the active Hageman factor reacts with a second clotting factor, possibly plasma thromboplastin antecedent, to form a potent clot promoting substance (684 413 621 535) The initial step in clotting then may be



A simplified version of the entire sequence of clotting is shown in Figure 1

In addition to its many clot promoting factors blood also has inhibitory properties which act to retard coagulation at several steps of the process For example plasma contains an enzyme like substance which inactivates Hageman factor after this has

been "activated" by contact with glass (412) Plasma also rapidly inactivates tissue thromboplastin (659) and thrombin (203) Teleologically these inhibitory devices may be important in preventing the formation or propagation of thrombi Whether any endogenous heparin plays a physiologic role in inhibiting clotting is disputed (466)

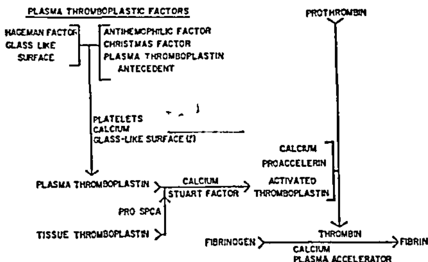


Figure 1 Some concepts of the physiology of clotting Proaccelerin is probably converted to accelerin during coagulation. The clot accelerating effect of glass may be mediated at several stages but a major role may be its activation of Hageman factor The inhibitors of the various clotting stages have been omitted from the diagram *(Modified from (534) with the kind permission of the Year Book Publishers Chicago)*

Blood also contains one or more proteolytic enzymes known collectively as *plasmin* or fibrinolysin which can digest fibrinogen fibrin proaccelerin antihemophilic factor and Christmas factor as well as such unnatural substrates as gelatin casein denatured hemoglobin and a variety of synthetic esters of amino acids (38 592) Plasmin is ordinarily inactive but can be activated *in vitro* by a variety of agents including chloroform streptokinase (a substance found in filtrates of certain beta hemolytic streptococci) tissue particles and urokinase (a principle in normal human urine) The enzyme may become active "spontaneously" in shed

boplastin, pro-SPCA and Stuart factor. Little is known about the mode of action of the pro SPCA, Stuart factor and proaccelerin, nor, indeed, of the order in which they act, probably a product of the interaction between thromboplastin, pro SPCA and Stuart factor reacts in turn with accelerin A tentative hypothesis can be represented in this manner

Prothrombin

Plasma thromboplastin → Stuart Factor / Calcium → Calcium, Proaccelerin, Activated thromboplastin → Thrombin

Pro SPCA

Tissue thromboplastin →

This formulation suggests that pro SPCA and Stuart factor alter thromboplastin which then converts prothrombin to thrombin The converse hypothesis is equally supportable, that is, that thromboplastin changes pro SPCA and Stuart factor into active substances which convert prothrombin to thrombin

The forces which maintain blood in a liquid state within the vessels but induce clotting when blood is shed are essentially unknown. The first step in coagulation appears to be the activation of Hageman factor (589 411, 546) This substance seems to be inert in the circulating blood but becomes active when exposed to glass or certain adsorbents Next, the active Hageman factor reacts with a second clotting factor, possibly plasma thromboplastin antecedent, to form a potent clot promoting substance (684 413 621, 535) The initial step in clotting then may be

I Hageman (inactive) —glass surface→ Hageman factor (active)

II Hageman factor (active) + plasma thromboplastin antecedent ——→ clot promoting substance

A simplified version of the entire sequence of clotting is shown in Figure 1

In addition to its many clot promoting factors blood also has inhibitory properties which act to retard coagulation at several steps of the process For example plasma contains an enzyme-like substance which inactivates Hageman factor after this has

of injury and form a mechanical plug which seals off the defect This may explain in part the greatly prolonged bleeding time observed *in many patients with thrombocytopenia* The platelets are attracted not only to the damaged vascular wall but to other platelets and as they adhere to each other they undergo a "viscous metamorphosis (723) in which they lose their identity and seem to break up Under these circumstances it is easy to imagine the liberation of substances with hemostatic properties Since platelets normally contain 5-hydroxytryptamine (serotonin) considerable speculation has arisen whether the release of this substance at the site of injury may contribute to hemostasis but the evidence supporting this attractive view is equivocal (728 605)

Purpura not only accompanies thrombocytopenia but also qualitative alterations in the platelets and even thrombocytosis a condition in which the concentration of platelets is greatly increased above normal. Although thrombocytopenia may be present in patients with certain infections hypersensitivity states or metabolic abnormalities bleeding may occur under these circumstances despite a normal platelet count Indeed purpura occurs in many disorders without obvious explanation Under such circumstances the bleeding phenomena are usually attributed to vascular injury often with scanty evidence Bleeding may accompany acquired or hereditary disorders of the vessels or of the surrounding mesenchymal tissue Yet the inadequacy of our classification becomes apparent as we learn that pseudohemophilia long believed to be a disorder of the vascular bed is often accompanied by defective blood clotting

Bleeding may result from a great increase in intracapillary blood pressure a classic example is the appearance of petechiae particularly in the eye after severe bouts of coughing or compression of the chest Changes in the viscosity of the blood and of the extravascular fluid such as occur in macroglobulinemia or cryoglobulinemia may also result in hemorrhage though how this comes about is unclear

The variety of bleeding states in which the pathogenesis is essentially unknown illustrates the need for more thorough studies of the ways in which blood cells are kept within their vessels and injuries to these vessels are repaired

blood for clotted plasma dissolves after a variable interval when incubated under bacteriologically sterile conditions Some evidence suggests that the clotting process itself may activate the enzyme, an observation with interesting implications Plasmin may also provide a long sought link between the clotting and immune mechanisms of the body for, like antigen antibody complexes, it appears to convert the first of the four recognized components of complement into a substance with enzymatic properties

A bleeding tendency may appear whenever a deficiency exists of any clotting factor with the inexplicable exception of Hageman factor Bleeding may also take place when plasma contains abnormal anticoagulant activity Finally under exceptional circumstances hemorrhage may be related to abnormal plasma fibrinolytic activity, presumably attributable to the action of plasmin

VASCULAR FACTORS IN THE CONTROL OF BLEEDING

When the integrity of the vascular wall is impaired a variety of hemorrhagic phenomena may appear The elements required to preserve the structure of the blood vessel are only poorly understood, and current views are based largely upon inferences derived from the study of pathologic bleeding For example the petechiae observed in areas of local anoxia suggest that oxidative processes are required for the maintenance of the vascular wall and the almost constant finding of bleeding in scurvy implies that vitamin C is needed to bind the capillary endothelial cells together

It is well known that the immediate control of bleeding from a small incised wound in the ball of the finger does not require the formation of a fibrin clot the "bleeding time" is usually normal in patients whose plasma lacks any detectable fibrinogen (496) Bleeding from this type of wound may be controlled in several ways Macfarlane (388) demonstrated by direct microscopy in human subjects that cutaneous capillaries normally contract when injured The extent of bleeding is also limited by the pressure which the extravasated blood exerts upon the outside of the vessel At the same time platelets quickly migrate to the site

Chapter II

SOME DIAGNOSTIC CONSIDERATIONS IN HEMORRHAGIC DISEASE

THE differentiation of the various hemorrhagic syndromes is based upon information derived from history, physical examination and laboratory studies A knowledge of the *duration of the illness* is usually of great value Patients with a hereditary coagulative abnormality or with "simple" purpura may not remember a time when they did not have hemorrhagic symptoms In other supposedly non hereditary disorders symptoms may persist for many years this may be the case in such syndromes as idiopathic thrombocytopenia purpura systemic lupus erythematosus thrombocythemia purpura hyperglobulinemia anaphylactoid purpura and autoerythrocyte sensitization On the other hand when a bleeding tendency first appears there is hardly a hemorrhagic disease which must not be considered Even the hereditary disorders of blood coagulation may not become manifest for many years and in such rare familial diseases as hereditary hemorrhagic telangiectasia and the Ehler Danlos syndrome symptoms often do not appear until late childhood or adult life

A careful evaluation of the *family history* is essential in the diagnosis of hemorrhagic disease Besides hemophilia many types of bleeding are of genetic origin current views on their mode of inheritance are summarized in Table II Often patients with lifelong hemorrhagic symptoms are unaware of any affected relatives such is the case in one-third or more of patients with hemophilia or Christmas disease Sometimes a disease may seem to skip generations though this may merely mean that it is manifest at a more advanced age in some individuals than in others Finally bleeding in the off spring of a patient with a hemorrhagic disorder need not be due to hereditary disease the newly born infant of a

SELECTED REFERENCES

22 Alexander B Coagulation hemorrhage and thrombosis *New Eng J Med 252* 432 484 526 1955

71 Biggs R and Macfarlane R G *Human Blood Coagulation and Its Disorders* Second Edition Oxford Blackwell Scientific Publications 1957

389 Macfarlane R G The Reactions of the Blood to Injury Blood Coagulation and Hemostasis Changes in the Blood Cells and the Activation of Fibrinolysis in *General Pathology* H Florey edit. Philadelphia, W B Saunders Co 1958

439 Milstone J On the evolution of blood clotting theory *Medicine 31* 411 1952

517 Quick, A J *Hemorrhagic Diseases* Philadelphia Lea & Febiger 1957

633 Stefanini M and Dameshek, W *The Hemorrhagic Disorders* A clinical and therapeutic approach, New York, Grune and Stratton 1955

is pin point red spots which usually turn brown during the week or two before they fade—suggest the presence either of thrombo cytopenia or of vascular disease they are unusual in hemophilia and other coagulative disorders Petechiae are particularly likely to be found in areas of the body subjected to high venous pressures or to constriction by the external pressure of tight clothing They are common in the dysproteinemias in scurvy and in other situations in which the integrity of the walls of the smallest vessels is impaired Petechiae or ecchymoses accompanied by erythema or urticaria occur in anaphylactoid purpura or autoerythrocyte sensitization, especially in the latter new lesions may be heralded by subjective sensations of tingling or stinging The presence of specific skin lesions may lead to a diagnosis of hereditary hemorrhagic telangiectasia the Ehlers Danlos syndrome or pseudoxanthoma elasticum

Bleeding into the subcutaneous, muscular or visceral tissues is particularly common in patients with coagulative defects or thrombocytopenia *Hemarthroses* are seen almost exclusively in the hereditary disorders of clotting particularly hemophilia and Christmas disease but for some unexplained reason have not been reported in parahemophilia Bleeding into joints also occurs in patients who have circulating anticoagulants directed against antihemophilic factor and in scurvy a disease easy to overlook nowadays Hemarthroses are sufficiently unusual in thrombocytopenia to suggest the presence of some additional abnormality *Diffuse swelling of the joints* not the result of intra articular bleeding brings to mind anaphylactoid purpura and persistent *arthralgias* may suggest systemic lupus erythematosus *Bleeding into the central nervous system* is said to be characteristic of thrombocytopenic purpura but hemorrhage into the brain or spinal cord is unfortunately common enough in hemophilia and Christmas disease and cerebrovascular symptoms occur in autoerythrocyte sensitization *Bleeding after dental extractions or surgery* complicates many hemorrhagic disorders but is distinctly unusual in anaphylactoid purpura or hereditary hemorrhagic telangiectasia

The patient s history must also be reviewed in a search for possible etiologic agents *A diet deficient in Vitamin C* may point

patient with thrombocytopenia may have transient purpura caused by passage across the placenta of a thrombocytopenia producing agent

TABLE II

FAMILIAL HEMORRHAGIC DISEASES

I Disorders Primarily of Males Transmitted as Sex Linked Recessive Traits

A Classic Hemophilia (Chapter III)
B Christmas Disease (or Plasma Thromboplastin Component Deficiency) (Chapter IV)
C Congenital Thrombocytopenia with Eczema and Repeated Infections (Chapter XV)

II Disorders of Both Sexes Transmitted as Autosomal Dominant Traits

A Plasma Thromboplastin Antecedent (PTA) Deficiency (Chapter VI)
B Vascular Hemophilia (Chapter XVII)
C Pseudohemophilia (Chapter XVII)
D Ehler Danlos Syndrome (Chapter XVIII)
E Osteogenesis Imperfecta (Chapter XVIII)
F Hereditary Hemorrhagic Telangiectasia (Chapter XIX)

III Disorders of Both Sexes Transmitted as Autosomal Recessive Traits

A Hageman Trait (Chapter V)
B Pro-SPCA Deficiency (Chapter VII)
C Stuart Factory Deficiency (Chapter VII)
D Prothrombin Deficiency (Chapter VII)
E Parahemophilia (Chapter VIII)
F Congenital Afibrinogenemia (Chapter IX)
G Familial Aplastic Anemia (Chapter XIII)
H Familial Aplastic Anemia with Congenital Anomalies (Fanconi s anemia) (Chapter XIII)

IV Disorders of Both Sexes in Which the Mode of Transmission Is Unclear or Multiple

A. Combined Hemophilia and Parahemophilia (Chapter X)
B Familial Thrombocytopenia with Congenital Anomalies (Chapter XIII)
C Familial Thrombocytopenia (Chapter XV)
D Thrombocytopathic Purpura (Chapter XVII)
E Pseudoxanthoma Elasticum (Chapter XVIII)
F Simple Purpura (?) (Chapter XXI)

The nature of the symptoms of bleeding is only of limited diagnostic help *Ecchymoses*—that is black and blue marks—occur in almost all bleeding disorders though they are conspicuously absent in hereditary hemorrhagic telangiectasia *Petechiae*—that

Several of the complications of *pregnancy* and *parturition* may be accompanied by a generalized bleeding tendency Hypofibrinogenemia occurs in association with the intra uterine retention of a dead fetus amniotic fluid embolism premature separation of the placenta or traumatic and usually self induced abortion The hemorrhagic manifestations of pre-eclampsia and eclampsia are of complex origin, thrombocytopenia is sometimes preeminent.

Bleeding is also a feature of many *hematologic disorders* Thrombocytopenia purpura may accompany aplastic megaloblastic or hemolytic anemias as well as acute or chronic leukemia Paradoxically patients with chronic myeloid leukemia or polycythemia may bleed despite thrombocythemia that is an excessive concentration of platelets Hemorrhagic manifestations are observed in patients with abnormal serum proteins including hyperglobulinemia cryoglobulinemia and macroglobulinemia

Patients with other *neoplastic diseases* may occasionally have a generalized bleeding tendency in different cases the result of thrombocytopenia or severe hypofibrinogenemia However cutaneous bleeding in advanced neoplastic disease may be unexplained by the usual laboratory tests and the physician may seek refuge in the unsatisfactory diagnosis of cachectic purpura

THE LABORATORY DIAGNOSIS OF HEMORRHAGIC DISEASE

In most cases of hemorrhagic disease the diagnosis rests ultimately upon the results of laboratory procedures The following paragraphs review the significance of certain tests in current use Others will be mentioned in association with the particular situations in which they may be useful. No attempt will be made to provide technical details which are well described in many recent books

Clotting Time in Glass Tubes Many methods have been devised to measure the lapse of time until shed blood clots These tests attempt to determine the intrinsic capacity of blood to coagulate in the absence of tissue thromboplastin The most satisfactory method is to measure the clotting time of venous blood. The blood must be drawn carefully to minimize the clot promoting effect of the tissues which the needle traverses to enter the vein The blood is transferred to a series of scrupulously clean

to a diagnosis of scurvy The list of *drugs* which may be responsi ble for purpura is endless Drug purpura may be associated with thrombocytopenia or with inflammation of the smallest blood vessels indistinguishable from the lesions of anaphylactoid purpura Very rarely, aspirin may induce purpura by coumarin like inhibition of the synthesis of the Vitamin K-dependent clotting factors Orally administered antibiotics may destroy the microorganisms which are the chief source of supply of this vitamin

A story of *injury* or *repeated surgical procedures* may precede the onset of autoerythrocyte sensitization Mention has been made of the appearance of petechiae in areas subjected to a sudden *increase in venous pressure* by paroxysms of coughing the straining of parturition or weight lifting (471) Petechiae may also occur in patients with severely thrombosed or varicose veins, particularly when these vessels are subjected to external pressure such as is exerted by tight garters (264)

Purpura is common in many systemic diseases Often the pathogenesis of bleeding is complex and the factors responsible for hemorrhage may vary from case to case For example pur puric manifestations, usually petechial in nature are observed in many *infectious diseases* The purpura may be related to thrombocytopenia which appears either at the height of the infection, as in epidemic hemorrhagic fever or during convales cence, more typical of the exanthemata In other infectious dis eases petechial eruptions have been attributed to direct vascular injury or to showers of microemboli In meningococcal disease, severe ecchymotic purpura may complicate the Waterhouse-Friderichsen syndrome *Purpura fulminans*, in which gangrenous cutaneous lesions are accompanied by severe disturbances of hemostasis is a rare but tragic sequel of infection, most often with beta hemolytic streptococci

In *liver disease* bleeding may be due to thrombocytopenia or to deficiencies of proaccelerin or of the Vitamin K dependent clotting factors The increased fibrinolytic activity of the blood of patients with chronic hepatic disease may exaggerate their bleed ing tendency Similarly, multiple factors may be responsible for the bleeding tendencies seen in *systemic lupus erythematosus renal failure amyloidosis, Cushing s syndrome, dysfunction of the thyroid gland* or *multiple myeloma*

glass tubes At measured intervals the first tube of the series is tilted until its contents are clotted then the second tube and so on until the contents of the last tube in the series is clotted To be meaningful the test must be carefully standardized It is probably preferable to measure the clotting time at 25°C rather than 37°C since the test is more sensitive to abnormalities at the lower temperature (419)

Many other techniques have been described to measure the clotting time The clotting time of capillary blood drawn into a capillary pipette is still widely used but is abnormally long only when the coagulative defect is gross Innumerable mechanical gadgets have been invented in an effort to avoid the subjective nature of the end point At present Hartert s thromboelastograph (159) is enjoying some popularity but this interesting device seems to offer no real advantage

The clotting time of normal blood is a function of the method used to interpret the results of this test one should be familiar with the values obtained in normal individuals in the same laboratory The clotting time in glass tubes is prolonged in many coagulative disorders but it is not a subtle test Normal values are found in uncomplicated thrombocytopenia and in many cases of mild hemophilia or Christmas disease Thus an abnormally long clotting time is more meaningful than a normal time

Clotting Time in Silicone-Coated or Lusteroid Tubes Measurement of the clotting time of venous blood in silicone-coated (308) or Lusteroid (536) tubes is highly useful to detect minor coagulative abnormalities Blood drawn into silicone-coated equipment and transferred to silicone-coated or Lusteroid tubes clots after a much longer interval than in glass since these surfaces promote clotting less effectively Preferably the clotting time is measured at 25°C rather than at 37°C because at the higher temperature the end point may be blurred by retraction of the clot before coagulation is complete

Silicone-coated tubes are less satisfactory than Lusteroid If the silicone coat is heavy the clotting time of normal blood is too long for practical use Thinner coats of silicone are difficult to apply evenly To obviate these difficulties I now use new uncoated Lusteroid tubes washed with Dreft The tubes offer a sur

TABLE III

DIFFERENTIATION OF SOME HEMORRHAGIC DISORDERS USUAL LABORATORY FINDINGS*

Disorders	*Clotting Time*	*Bleeding Time*	*Tourniquet Test*	*Prothrombin Time*	*Serum Prothrombic Activity*	*Special Tests*
Classic hemophilia	Long	Normal	Normal	Normal	High	Corrected by BaSO absorbed plasma
Christmas disease	Long	Normal	Normal	Normal	High	Corrected by serum
Plasma thromboplastin antecedent (PTA) deficiency	Long	Normal	Normal	Normal	High	Corrected by serum or BaSO adsorbed plasma
Hageman trait	Long	Normal	Normal	Normal	High	Corrected by serum or BaSO adsorbed plasma
Parahemophilia	Long	Normal	Normal	Long	High	Corrected by fresh $BaSO_4$ adsorbed plasma
Pro-SPCA deficiency	Variable	Variable	Normal	Long	Normal	Corrected by serum or aged plasma
Stuart factor deficiency	Variable	Variable	Normal	Long	High	Corrected by serum or aged plasma
Hypoprothrombinemia	Normal	Normal	Normal	Long	Normal	Corrected by aged plasma
Afibrinogenemia	Infinite	Variable	Normal	Infinite	Normal	Not corrected by thrombin
Thrombocytopenia	Normal	Long	Positive	Normal	High	Thrombocytopenia impaired clot retraction
Vascular hemophilia	Long	Long	Normal	Normal	High	Corrected by BaSO adsorbed plasma
Thrombocytopathic purpura	Normal	Long	Normal	Normal	Variable	Normal platelet count clot retraction may be impaired
Pseudohemophilia	Normal	Long	Normal	Normal	Normal	Normal platelet count and clot retraction

* Modified from (534) with the kind permission of the Year Book Publishers Chicago
Distinguished by special te ts

initial stages of clotting as hemophilia Christmas disease and Hageman trait in which it permits rapid and accurate diagnosis

Thrombin Time The final stages of the clotting process the conversion of fibrinogen to fibrin may be tested by measuring the thrombin time that is the clotting time of a mixture of oxalated or citrated plasma and bovine thrombin A measured amount of thrombin is added to the plasma, and the clotting time of the mixture is measured in a uniform way There is no arbitrary standard for the normal thrombin time so that one must always compare the plasma to be tested with a normal plasma The thrombin time should be performed with freshly prepared plasma since storage alters the result

The thrombin time is abnormally long in the normal newborn infant and in hepatic disease systemic lupus erythematosus toxemia of pregnancy, macroglobulinemia and multiple myeloma (532) The mechanisms responsible for the abnormal thrombin time are not clear In some cases the prolonged thrombin time is due to qualitative alterations in fibrinogen or to a decreased concentration of this protein In others an endogenous or exogenous circulating anticoagulant such as heparin may lengthen the thrombin time In still other cases the prolonged thrombin time seems to be related to changes in other constituents of the plasma

Prothrombin Time The middle stages of the clotting process are most readily studied by the measurement of the one stage prothrombin time first introduced by Quick (523) In this test, tissue thromboplastin is added to oxalated or citrated plasma and the mixture is recalcified The prothrombin time is the clotting time of this mixture It has been recommended that the potency of the thromboplastin be such that the normal one stage prothrombin time will be twelve seconds When this is the case a decrease of 50 per cent in the concentration of prothrombin lengthens the prothrombin time by only three seconds Relatively greater changes in the prothrombin time will be obtained with *somewhat weaker suspensions of thromboplastin making it easier* to recognize minor abnormalities

Many laboratories compare the prothrombin time of the patient under study with only one normal individual However there is considerable variation among supposedly normal subjects so that

face intermediate in its clot promoting effects between a heavy coat of silicone and a Pyrex surface Measurement of the clotting time in Lusteroid tubes has been satisfactorily reproducible

The silicone or Lusteroid clotting time is often abnormally long in cases in which the clotting time in glass tubes is normal. Indeed it is unusual for the clotting time to be normal in Lusteroid tubes when a coagulative defect is demonstrated by other techniques

Recalcified Plasma Clotting Time For many purposes, measurement of the clotting time of recalcified citrated or oxalated plasma is a useful procedure The recalcified clotting time is usually prolonged only when severe coagulative abnormalities are present

If the recalcified clotting time of a patient s plasma is long, the specific defect responsible may be determined by mixing his plasma with that of a patient with a known abnormality If the two plasmas are mutually corrective each presumably lacks a different factor If they are not mutually corrective the two plasmas probably lack a factor in common For example, a plasma is known to lack antihemophilic factor but to have normal amounts of Christmas factor A mixture of this plasma and a plasma under test clots in a normal time Presumably, then the plasma under test contains antihemophilic factor This technique permits the diagnosis of most coagulative abnormalities even in cases in which the recalcified clotting time is normal These tests require a collection of plasmas with recognized defects and known to have long recalcified clotting times One can substitute for these abnormal plasmas plasmas in which the abnormality is simulated by laboratory manipulation However the use of such artificial plasmas may be hazardous for unsuspected artifacts may confuse the results

On the other hand the storage of abnormal plasmas is also hazardous since even at -70°C antihemophilic factor and proaccelerin gradually deteriorate particularly in oxalated plasma The use of citrate as an anticoagulant minimizes the effects of deterioration

The recalcified clotting time of a mixture of normal and abnormal plasmas is one of the most sensitive diagnostic measures It is especially helpful in the diagnosis of such disorders of the

When venous blood is incubated in glass tubes without the addition of an anticoagulant, its prothrombin is gradually converted to thrombin The rate at which thrombin forms depends upon the rate at which thromboplastic activity develops and then reacts with prothrombin When enough thrombin is formed the blood clots At this time not all of the prothrombin has been changed to thrombin indeed for some time after clotting has been completed the serum still contains appreciable amounts of prothrombin Tests of prothrombin "consumption" measure the residual prothrombin remaining in serum at an arbitrary time after the blood was placed in glass tubes Thus these tests are overall measures of the rate at which thromboplastic activity develops and the rate of the consequent conversion of prothrombin to thrombin (518 631 31) For example, in hemophilic or thrombocytopenic blood the evolution of thromboplastic activity is believed to be slower than in normal blood Reflecting this the serum prothrombic activity of such blood is higher than normal This is often stated in the converse way that prothrombin "consumption" is impaired

Properly performed measurement of serum prothrombic activity is often useful in the diagnosis of disorders of coagulation Meticulous technique is required The blood is incubated in Pyrex tubes free of silicone After an arbitrary period the clotting process is stopped by adding an anticoagulant and time then allowed for the thrombin which has evolved to be inactivated. The concentration of prothrombin which remains in the serum is then determined by a method which measures this substance specifically and is uninfluenced by other clotting factors Abnormal results are obtained in deficiencies of the plasma clotting factors (except prothrombin fibrinogen and possibly pro SPCA) in qualitative or quantitative platelet disturbances and in the presence of certain circulating anticoagulants However the test for serum prothrombic activity is not sensitive and normal values may be obtained in patients with partial deficiencies of clotting factors thought to influence the determination

Thromboplastin Generation Test In 1952 Biggs and Douglas (69) introduced a test designed to measure the earliest stages of clotting the evolution of thromboplastic activity Serum citrated

a doubtful result should be checked against several normal plasmas Expression of the results of the prothrombin time in terms of the concentration of prothrombin is inaccurate, since the test measures a number of variables, and a less committal term such as apparent prothrombic activity may be more satisfactory The prothrombin time is abnormally long when there is a deficiency of any factor needed for thrombin formation in the presence of tissue thromboplastin–prothrombin, proaccelerin pro-SPCA, or Stuart factor It is prolonged when the concentration of fibrinogen is low, in afibrinogenemia the blood is incoagulable The prothrombin time is also long in the presence of an anticoagulant inhibiting the middle stages of clotting Heparin interferes with this phase of clotting as well as inhibiting the formation of fibrin, and an anticoagulant with this property has also been described in systemic lupus erythematosus

When the one stage prothrombin time is abnormal the plasma can be analyzed to determine which factors are responsible for the abnormality The principle underlying this analysis is to mix small amounts of the plasma to be tested with reagents containing all the clotting factors except the one to be measured The prothrombin time of this mixture is then determined

Partial Thromboplastin Time Langdell and his associates (344) have popularized the measurement of the recalcified clotting time in the presence of crude cephalin mixtures derived either from mammalian brain or from soy beans The test is performed in the same way as the prothrombin time except for the substitution of the crude cephalin for tissue thromboplastin The results of this test may be abnormal in cases in which the recalcified clotting time is normal A prolonged partial thromboplastin time has been observed in patients deficient in antihemophilic factor, Christmas factor, Hageman factor plasma thromboplastin antecedent Stuart factor and proaccelerin, but the test gives normal results in cases of pro SPCA deficiency (561) The test is deceptively simple for great care must be exercised to obtain consistent results Although of great help in detecting minor coagulative abnormalities it is not yet satisfactory for general use

Serum Prothrombic Activity (Prothrombin Consumption Test)

the theoretic basis of the thromboplastin generation test has been questioned The principle problem is the difficulty of preparing the ingredients of the incubation mixture free of prothrombin There is evidence that in addition to thromboplastin accelerin and thrombin are generated in the incubation mixture These theoretic considerations do not challenge the great utility of the thromboplastin generation test both for diagnosis and research The thromboplastin screening test is not as useful in the differ ential diagnosis of clotting disease but is a sensitive indicator of the presence of mild coagulative abnormalities

Bleeding Time Many techniques have been devised to test an individual s capacity to seal off a small wound (187) One simple method is to incise the ball of a finger with a sterile scalpel blade In normal individuals bleeding usually begins immediately in creases in intensity for a minute or two and then within three to seven minutes stops A result can be considered to be abnormal only in the light of the experience of the particular laboratory in which the test is performed Sometimes bleeding does not stop for many minutes or even hours I discontinue the test if bleeding continues for more than fifteen minutes since the patient becomes understandably agitated The application of firm pressure with a Band Aid is a simple way to stop the bleeding In some labora tories the ear lobe is incised instead of the ball of the finger However if the patient bleeds unduly it is difficult to stop hemorrhage from an ear lobe

The bleeding time varies considerably even in the same in dividual tested repeatedly within a few minutes In part this variability results from an inability to control the depth of the incision the thickness of the skin and the environmental tempera ture For these reasons a long bleeding time is much more signifi cant than a normal result The bleeding time is abnormally long in patients whose platelets are defective The test is positive in patients with thrombocytopenia thrombocythemia or the throm bocytopathic purpuras characterized either by defective clot re traction or poor prothrombin consumption The bleeding time is also prolonged in cases of vascular hemophilia pseudohemophilia and macroglobulinemia Positive tests are unusual in patients with coagulative disorders even in patients with afibrinogenemia the

plasma, and platelets are prepared from the blood of the patient to be tested and from a normal individual The plasma is adsorbed with aluminum hydroxide to remove prothrombin pro-SPCA, Stuart factor and Christmas factor A mixture of platelets, diluted serum, diluted adsorbed plasma and calcium is prepared This incubation mixture, containing all of the recognized clotting factors except prothrombin, is incubated and at intervals samples are removed and added to normal platelet deficient plasma ("substrate") Biggs and Douglas postulated that "thromboplastic activity develops in the incubation mixture and that the second step measures this activity Thus

Stage One Serum (containing pro SPCA, Stuart factor, Christmas factor, plasma thromboplastin antecedent and Hageman factor) + adsorbed plasma (containing proaccelerin, antihemophilic factor, plasma thromboplastin antecedent and Hageman factor) + platelets + calcium ⟶ Thromboplastin

Stage Two "Thromboplastin + platelet deficient plasma (containing prothrombin, fibrinogen and other clotting factors) + calcium ⟶ evolution of thrombin and formation of a clot

By testing successive samples of the incubation mixture, the rate of evolution of thromboplastic activity and the intensity of the activity which develops are measured

This test has been further modified by substituting for the platelets cephalin" derived either from mammalian brain or soy beans This modification precludes an evaluation of platelet function but facilitates preparation of the reagents needed for the test A second modification of great usefulness is the thromboplastin screening test, devised by Hicks and Pitney (282) In this test, the incubation mixture consists merely of diluted plasma, cephalin and calcium The clot promoting activity which develops in this mixture is measured by the same technique used for the second stage of the thromboplastin generation test

In practice the thromboplastin generation test has been most useful in the diagnosis of deficiencies of the various clotting factors except prothrombin and fibrinogen For example in hemophilia thromboplastin generation is impaired, the defect is corrected by adding normal adsorbed plasma to an incubation mixture containing hemophilic serum and platelets However

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wound may stop bleeding within a normal time However, in patients with severely defective clotting bleeding may start again when the patient flexes his finger or otherwise disturbs the wound

Capillary Fragility Tests Many methods have been devised to determine the ease with which capillaries disrupt or become permeable to red blood cells These methods fall into two general types In one the capillaries are subjected to 'negative" pressure by the application of suction to an area of skin the number of petechiae which appear in the tested area is taken as an index of the fragility of the capillaries (136) In the second "positive" pressure method a blood pressure cuff, applied to the upper arm is inflated below arterial systolic pressure for an arbitrary period (241) Our technique is to inflate the cuff at 100 mm of mercury for five minutes or, if the systolic pressure is below 100 mm to 90 mm for seven minutes The results of this tourniquet test are usually read by counting the number of petechiae in a predesignated area on the volar surface of the forearm

In practice, both negative and positive pressure methods give erratic results despite vigorous efforts at standardization The same individual may react differently to successive trials of the same procedure Often grossly different results are obtained by the application of suction to two adjacent areas of skin Similarly, the tourniquet test may be difficult to interpret because few or no petechiae appear upon the volar surface of the forearm yet the dorsum of the hand and wrist may be peppered with large petechiae

In general, positive capillary fragility tests are particularly common in patients with thrombocytopenia but they have been reported in many other types of purpura nullifying the diagnostic value of the procedure Moreover the tests may give positive results in supposedly normal individuals In my experience this variability has made capillary fragility tests almost useless

Routine Pre Operative Bleeding and Clotting Times Determination of the bleeding and clotting time is a common practice prior to surgery particularly tonsillectomy I do not believe that these procedures provide an adequate safeguard against hemorrhage due to an unsuspected coagulative disorder (166) Much more to the point is a careful history to uncover previous symp

toms of a bleeding tendency This history should be respected regardless of the results of routine laboratory tests All too often, the physician or dentist, having found normal bleeding and clotting times ignores the history and proceeds with surgery Only when the patient then bleeds severely is the true diagnosis determined

One test should be done prior to any surgical procedure, particularly in children A cover slip blood smear should be examined to be sure that an adequate number of platelets is present Transient thrombocytopenia without symptoms is a common sequel of infection in children and may lead to serious hemorrhage if the patient is subjected to surgery A second test one might use is the prothrombin time for rarely a patient with no history of bleeding has an abnormally long prothrombin time and will bleed if challenged by surgery

SELECTED REFERENCES

71 Biggs R and Macfarlane R G *Human Blood Coagulation and Its Disorders* 2nd Edition, Oxford, Blackwell Scientific Publications 1957

108 Cartwright, G E *Diagnostic Laboratory Hematology* 2nd Edition New York, Grune and Stratton 1958

158 deNicola P *The Laboratory Diagnosis of Coagulation Defects* Springfield Charles C Thomas 1956

633 Stefanini M and Dameshek, W *The Hemorrhagic Disorders a Clinical and Therapeutic Approach* New York, Grune and Stratton 1955

661 Tocantins L M edit *The Coagulation of Blood Methods of Study* New York, Grune and Stratton 1955

Chapter III

CLASSIC HEMOPHILIA

CLASSIC hemophilia a disease confined almost exclusively to males is manifested primarily by bleeding into soft tissues and joints The commonest of the major hereditary disorders of coagulation hemophilia is the expression of a deficiency in plasma of antihemophilic factor (479) Within the last few years it has become evident that other diseases particularly Christmas disease can be distinguished from classic hemophilia only in the laboratory One must therefore be careful not to attribute to classic hemophilia any particular quality described prior to its differentiation from other disorders Hemophilia will serve to illustrate many of the problems common to patients with hemorrhagic disease

Hemophilia is a rare disease I have knowledge of about 75 cases in metropolitan Cleveland an incidence of about one case for every 20 000 inhabitants The life history of the typical severe hemophiliac is marked by recurrent bouts of bleeding Often the bleeding begins spontaneously while at other times it appears to be the exaggerated response to trivial injury Hemophilia may be manifest at birth the defect is demonstrable in blood obtained from the umbilical vein (168 270 534) Rarely the infant bleeds fatally from injuries sustained at childbirth (432) Bleeding from the umbilical stump is unusual More commonly the disease becomes evident when severe bleeding follows circumcision surprisingly some patients undergo this procedure without difficulty

During his infancy the hemophiliac s parents gradually become aware of his bleeding tendency Unexplained hematomas may appear anywhere and may reach enormous proportions A hematoma larger than an orange is not unusual These gradually disappear without therapy The infant may have ecchymoses often

after little or no obvious injury but petechiae are rare (516) As the hemophiliac begins to crawl and walk episodes of bleeding become more frequent He may have epistaxes gastrointestinal or urinary tract bleeding or hemarthroses Trivial injuries may be followed by prolonged hemorrhage A common site of bleeding in infancy is the frenum of the upper lip which may be cut accidentally during a fall Any form of surgery may be disastrous

Hemorrhage during the eruption or loss of deciduous teeth is usually no greater than in normal children but occasionally the eruption of permanent teeth may be accompanied by severe bleeding Bleeding at the gingival margins is common and may contribute to the characteristically poor dental hygiene of hemophiliacs As a result dental extraction is often necessary and may be followed by severe protracted and even fatal bleeding

Hemarthroses usually become evident when the child begins to walk (149) Bleeding into joints occurs in about half of cases particularly in those with the greatest laboratory abnormalities The typical severely affected hemophiliac comes to the doctor on crutches Although any joint may be involved those most often affected are the knees ankles and elbows (658) At first the joint is stiff and painful It rapidly becomes swollen warm to the touch and if the capsule is markedly distended exquisitely tender The muscles crossing the joint may be in protective spasm Discoloration around the joint is surprisingly uncommon When bleeding stops the blood within the joint is gradually absorbed and mobility is slowly regained However once a joint has been the site of hemarthrosis it is more likely to bleed again and as the process repeats itself permanent and crippling deformities ensue The peculiar susceptibility of joints to bleeding which is so characteristic of hemophilia and Christmas disease is not understood hemarthrosis is unusual in other hemorrhagic diseases Astrup and Sjølin (38a) relate the tendency to intraarticular bleeding to the low thromboplastic activity of synovial and joint capsular tissue Normally bleeding into the joints may be controlled by the blood s intrinsic capacity to clot but in hemophilia this capacity is defective

Subsequent to bleeding vascular hyperplasia of the synovia and thickening of capsular and pericapsular tissues may develop

resulting in a loss of elasticity of the tissues around the joint, scarring and contracture The synovial tissues are impregnated with iron The cartilages within the joint become thin and eroded and are invaded by a panus of hyperplastic vascular synovial and subsynovial tissues Granulation tissue also invades the joint from the marrow space Cysts form as the result of enlargement and coalescence of Weichselbaum s lacunae destruction of subchondral bone and cartilage by the vascular connective tissues, and in cancellous bone breakdown of atrophic bony trabeculae (162) The collapse of these cysts may produce angular deformities particularly in the knee Angular deformities and shortening of the bone may also arise from premature closure of the epiphyseal plate In subchondral bone, the severe atrophy of the bony trabeculae may lead to fracture compression and flattening of articular surfaces After repeated hemarthroses the epiphyses may increase irregularly in width resulting in the knobby appearance the incongruity of the articular surfaces restricted motion and eventually fixed deformity of the typical hemophilic joint A serious complication fortunately rare in my experience, is destruction of the head of the femur with shortening of the involved leg sequelae of bleeding into the hip (74) Surprisingly bony ankylosis is unusual

Sometimes joint deformities may follow massive hemorrhage into the muscles rather than into the joint space itself In the lower extremities the commonest deformity resulting from this type of soft tissue hemorrhage is flexion contracture of the knee and equinus deformity of the ankle Occasionally flexion deformities of the hip may follow hemorrhage into the psoas muscles Finger deformities resembling "claw hand may be a sequel to palmar hemorrhage

The roentgenographic appearance of hemophilic joints is characteristic (317) During the acute phase a diffuse haziness sharply demarcated from the surrounding tissues may be observed The joint space is distended Later the changes may simulate osteoarthritis The bony ends of the joints may broaden and the joint spaces become narrow The articular surfaces grow irregular in appearance with punched out defects reminiscent of gout In severe cases the articular surface may be totally de

stroyed The bony cysts which may be present in subchondral or cancellous bone look like soap bubbles and x rays may demonstrate the deformities which follow their collapse The increased density of the synovial and subcapsular tissues may demarcate the affected joint sharply and calcium deposits may be seen in these soft tissues The patella presents a typical appearance, for the ends tend to become blunted

Hemorrhage into soft tissues sometimes causes occlusion of the arterial blood supply resulting in atrophy or even gangrene (633) The gangrenous part sloughs off without undue bleeding Bleeding into the soft tissues of the floor of the mouth the neck or the mediastinum may cause death from asphyxiation unless intubation or tracheotomy is performed (623) Soft tissues distended and damaged by a collection of blood may become necrotic and develop persistent and occasionally lethal infections

Hematuria is a commonplace in the severe hemophiliac the bleeding arising from any point of the urinary tract Severe colic, presumably from distention of a ureter is frequent Hematuria tends to be persistent each episode lasting days or weeks despite therapy which in other situations would be considered adequate

Other forms of intra abdominal bleeding are common Bleeding into the psoas muscles may simulate acute appendicitis or cause compression of the branches of the femoral plexus with paralysis of the corresponding muscles or pain in the abdomen and leg Intraperitoneal bleeding may cause confusion with any of the inflammatory disorders of the abdomen Under such conditions exploratory laparotomy may well be fatal Hemothorax or hemopericardium may be equally perplexing

Bleeding into the nervous system is not as rare as one would gather from most descriptions (16) Strategically located hematomas in soft tissues may compress or otherwise damage peripheral nerves sometimes leading to permanent damage Occasionally there may be epidural subdural, subarachnoid or focal bleeding into the central nervous system Douglas and McAlpine (182) observed neurological lesions in five of seventy five hemophiliacs including one ten year old boy who developed right hemiplegia following a spontaneous cerebral hemorrhage and another who had compression of the spinal cord by a hematoma

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The burdens which hemophilia imposes upon the personality are borne in various ways The child s parents are continually oppressed by his disease and may be obsessed with guilt for their responsibility The mother may sense her husband s accusation that she has caused the disease and therefore the family s troubles (22) Sometimes she will hide the fact that she has a hemophilic child from her relatives or will pretend to her husband that she does not have a family history of hemophilia under such circumstances life seems almost unbearable for her All these forces play upon the developing child Moreover perpetual admonishments to be careful soon make him fear ridden The frequent hospitalizations and the innumerable venipunctures and intravenous injections add to his difficulties Often the patient seems immature as if his parents had not allowed him to grow up His schooling is sporadic and his parents may not realize the importance of preparing him for a suitable occupation in adult life

As he grows older the hemophiliac feeling stigmatized may withdraw into himself shunning the company of others He fears any relationship with the opposite sex and if he marries he dreads passing the trait to his children The depression and the chronic feeling of shame may lead to suicide one of my patients slashed his wrists Other patients attempt to deny the existence of their disease Four of my patients emulating the Spanish infante race sports cars or motorcycles with more enthusiasm than wisdom Some hemophiliacs wisely choose a sedentary occupation while others tempt fate and seek jobs which are intrinsically hazardous An appreciation of the emotional problems which beset these patients is clearly helpful in the management of their disease

The hereditary nature of hemophilia has always held a peculiar fascination for both physicians and the laity In part this is because of the presence of hemophilia in the royal families of Europe These regal bleeders of whom the most momentous was the last Tsarevich were descendants of Queen Victoria of England (607) The pattern of inheritance in her family was typical of that for hemophilia in more plebian circles A hemophiliac s sons are all normal and cannot transmit the disease to their offspring On the other hand the hemophiliac s daughters are all carriers of the trait though they usually do not have a bleeding tendency In turn half of a carrier s sons are hemophiliacs and

subsequent to a fall One of my patients had transient hemiplegia followed during the subsequent five years by repeated epilepti form convulsions Seizures subsequent to intracranial hemorrhage have also been described by Jordan (317)

Despite this pessimistic description, the patient with severe hemophilia does not bleed continually Instead bouts of bleeding alternating with periods of freedom are the rule Bleeding into several sites is common during any one relapse as if the hemostatic mechanisms suddenly deteriorate No satisfactory explanation for this observation has been forthcoming One of my patients insists that emotional disturbances precipitate bleeding a view also expressed by Poinsard (500), but without objective foundation As the patients grow older they tend to be more careful perhaps accounting for the decreased frequency of bleeding with increasing age (36) However, time may play a more fundamental role since epistaxes frequent in childhood become uncommon or disappear during the teens

Fortunately not all hemophiliacs present the grim picture I have described A third or more of patients have a much milder form of the disease (247) Some may have no symptoms until they are four or five years of age or older Bleeding may follow dental extractions tonsillectomy or other surgical procedures but may not occur from everyday injuries Such patients may have severe and temporarily incapacitating hematomas in soft tissues but hemarthroses are rare and permanent changes in the joints rarer still Often the diagnosis of mild hemophilia is difficult to make and both patient and physician tend to doubt the presence of the disease One of our patients was in his seventies before it was firmly established that he was a bleeder

By and large the affected members of a hemophilic clan have about the same degree of difficulty (71) Exceptionally, a patient with mild hemophilia will describe relatives who have died of the disease in some of these cases exsanguination followed surgery for which adequate preparation had not been made The appearance of a circulating anticoagulant (Chapter XI) may greatly increase the severity of hemophilia and make the patient resistant to therapy With these exceptions one can judge with reasonable accuracy the severity of the disease in the affected relatives of a hemophiliac

This description gives the impression that all patients with hemophilia have a characteristic family history In fact this is true in only about half or three fourths of cases (613) The remaining seem to arise *de novo* In part this may be due to the difficulty in obtaining accurate family histories Particularly in

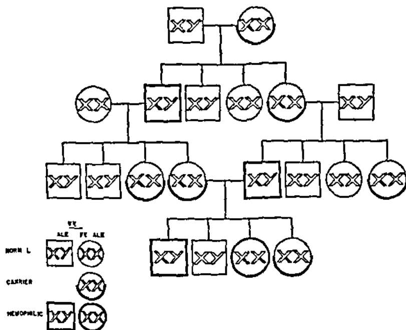


Figure 2 The pattern of inheritance in hemophilia The so-called sex chromosomes are represented schematically as Xs and Ys in accordance with convention The pattern of inheritance in Christmas disease is identical. *(Reprinted from (534) with the permission of the Year Book Publishers Chicago)*

mild cases even the immediate family tree may be inaccurate In other instances hemophilia may have arisen from the spontaneous mutation of a gene Although estimates of the frequency of spontaneous mutation have been published, the evidence on which such calculations are based is not adequate for the purpose

The implication has been made that the synthesis of antihemophilic factor is determined by a single gene located on the X

half of her daughters are carriers Her other children will be normal, and will not transmit the disease to subsequent generations

These hereditary relationships are readily explained by classic genetic theory An individuals sex is determined by the inheritance of a pair of sex chromosomes one from each parent The female inherits an X chromosome from each parent, so that the pair consists of two X chromosomes The male, on the other hand, inherits an X chromosome from his mother, and a much smaller Y chromosome from his father

The synthesis of antihemophilic factor depends upon the presence of a gene located in the portion of the X chromosome which has no counterpart in the Y chromosome Classic hemophilia is caused by the inheritance of an abnormal recessive allele of this gene A hemophilic male inherits from his mother an X chromosome containing the abnormal allele and from his father a normal Y chromosome The presence of the abnormal allele unopposed by a normal allele results in classic hemophilia If his wife is normal the hemophiliacs sons will inherit his normal Y chromosome and their mothers normal X chromosome these sons will neither have hemophilia nor transmit the trait to their progeny The hemophiliacs daughters will inherit an abnormal X chromosome from him and an X chromosome from their mother If their mother is normal the hemophiliacs daughters will thus have one normal X chromosome and one bearing the abnormal allele The normal gene behaves as a dominant and its abnormal allele as a recessive These daughters then will all carry the trait but will usually not have the overt disease Married to normal males the carriers will transmit the hemophilic X chromosome to half their sons who will be hemophiliacs and to half their daughters who will be carriers Only if a hemophilic male marries a female carrier can his daughters inherit the full blown disease for she may inherit the abnormal X chromosome from each parent A hypothetical family tree, illustrating these principles is given in Figure 2 Hemophilia comparable in all known respects to that of man occurs in dogs This has made it possible to confirm these observations in the statistically more comfortable progeny of hemophilic carriers of this species (246)

human preparations are highly unstable The instability of anti hemophilic factor is also manifest by its erratic disappearance during the storage of blood in a blood bank

Although its exact function is unknown antihemophilic factor, along with Hageman factor, plasma thromboplastin antecedent Christmas factor platelets and calcium, is concerned in the development of thromboplastic activity In this process it is possible that antihemophilic factor and Christmas factor interreact, to form a product which reacts with platelets (54) Antihemophilic factor disappears rapidly during clotting and is absent from serum (178 248)

In the opinion of most observers the fundamental defect in uncomplicated hemophilia is a deficiency of antihemophilic factor (244) An alternative view (663 664), that hemophilic plasma inhibits the action of antihemophilic factor, does not account for the corrective effect of normal plasma both *in vivo* and *in vitro* Inhibitory activity against antihemophilic factor may be found in the blood of certain hemophiliacs but such "circulating anticoagulants" are not detectable in the majority of cases (Chapter XI)

The concentration of antihemophilic factor in a given plasma can be measured by testing its effect upon known hemophilic plasma No absolute standard exists The antihemophilic activity of normal plasma varies from individual to individual as much as three-fold but in any given subject is more constant from time to time In hemophilia the degree of deficiency of antihemophilic factor roughly parallels the severity of symptoms (247 520) In severe hemophilia the plasma behaves as if it is devoid of antihemophilic factor while in milder cases activity as high as 5 or 10 per cent of the average normal plasma may be present (247)

The results of laboratory tests reflect these differences in anti hemophilic activity The clotting time of venous blood measured in glass tubes may be normal or prolonged depending upon the magnitude of the defect (428) A normal clotting time is observed in a third or more of cases of proved hemophilia (168) The clotting time is more likely to be abnormal if measured in silicone coated or Lusteroid tubes but even this test may be normal in

chromosome The possibility exists that at least one or two other genes influence the synthesis of this protein (498) Evidence in support of this has accumulated from the study of patients with vascular hemophilia (Chapter XVII) and coincident hemophilia and parahemophilia (Chapter X)

LABORATORY STUDIES IN CLASSIC HEMOPHILIA

The essential lesion in patients with classic hemophilia is a defect in blood clotting The alteration in the clotting mechanism is localized to an early stage of clotting, the development of thromboplastic activity The thrombin time which tests the effect of pre formed thrombin on fibrinogen and the prothrombin time which measures the rate thrombin forms upon addition of tissue thromboplastin are normal However when hemophilic blood is incubated by itself in glass tubes thrombin evolves more slowly than normally (93) The retarded formation of thrombin may be determined directly or may be inferred by measuring the prothrombin content of serum In hemophilia prothrombin disappears from clotted blood more slowly than normally, that is prothrombin "consumption" is poor (93 515) For example by one method less than one-fourth of its original content of prothrombin remains in normal blood within an hour after it is drawn On the other hand in severe hemophilia no significant decrease in the concentration of prothrombin is detectable at this time, even though clotting may have occurred The deficient formation of thrombin seems to reflect an impairment in the development of intrinsic thromboplastic activity in hemophilic blood Consistent with this the results of the thromboplastin generation test of Biggs and Douglas are abnormal (69)

In hemophilia the platelet count is normal. The abnormality in coagulation can be demonstrated in the cell free plasma of hemophiliacs and can be corrected by the addition of small amounts of normal plasma (478) The corrective property is localized to a fraction of normal plasma antihemophilic factor The properties of antihemophilic factor have been studied intensively Its site of synthesis is unknown (243) It is a protein associated with the euglobulins of plasma and can be prepared in high concentration from human and animal blood However most

severely after dental extraction or surgery These patients have told us that their story was disbelieved because the results of routine testing were normal

THE CARE OF THE PATIENT WITH HEMOPHILIA

The treatment of an acute episode of bleeding in a hemophiliac can be divided into three phases In the first place one must prevent shock from exsanguination Severe blood loss is uncommon in hemophilia but may occur as the result of accident the extraction of teeth or other surgery or bleeding from the gastrointestinal tract Blood replacement should be pursued in the same energetic fashion as in other cases of blood loss However, freshly drawn blood should be used as soon as it is available since it is richer than stored blood in antihemophilic factor Local measures to control severe blood loss including the application of pressure and hemostatic agents to the site of bleeding are of great value Blood on the surface of the wound should be wiped away to allow the hemostatic agent to come in direct contact with the oozing surface (71) The hemostatic agent with which I have had the most experience is bovine thrombin applied at a concentration of 1 000 National Institutes of Health units per cc with a dropper or on a pledget of absorbable material (10) Biggs and Macfarlane (71) comment favorably upon the use of Russell s viper venom as a hemostatic agent and others have used tissue thromboplastin Bleeding from the nose has often been treated by the application of a cautery but this has only been disastrous in my experience More effective control of bleeding can be gained by pressing a pledget of absorbable material soaked in thrombin against the bleeding point (391)

The second phase of treatment is temporary correction of the hemostatic defect by the administration of blood or plasma containing antihemophilic factor Sometimes adequate hemostasis can be achieved by raising the concentration of this factor to 5 or 10 per cent of the average normal (22) but bleeding may not be controlled until the concentration is 30 per cent of normal or higher (15) Such levels of antihemophilic factor are all but impossible to achieve by the transfusion of whole blood both because of the volume required and because of the difficulty in

individuals with mild but demonstrable hemophilia In moderate or severe hemophilia, serum prothrombic activity is abnormally high, mention has already been made that in severe cases, the prothrombic activity may be 100 per cent that of plasma one hour after the blood has been drawn Again in mild cases a normal value may be obtained (626 633) The results of the thromboplastin generation screening test (282) and thromboplastin generation test are abnormal The defect in the thromboplastin generation test is corrected by substituting normal aluminum *hydroxide adsorbed plasma for the patient s adsorbed plasma* in the incubation mixture The diagnosis is established by demonstrating that the patient s plasma does not correct the defect in the blood or plasma of hemophiliac and *vice versa* The technique used varies with each laboratory s particular experience For example one may test the capacity of the patient s plasma to correct the abnormal clotting time (428), prothrombin consumption (623) thromboplastin generation (69) or partial thromboplastin time (344) of known hemophilic blood or plasma

When fresh hemophilic blood or frozen hemophilic plasma is not available the diagnosis can be made by preparing crude antihemophilic factor from normal plasma This fraction should correct the patient s defect *a similar fraction prepared from the patient s plasma should be inert* Appropriate measures must be taken to rule out the presence of a circulating anticoagulant which might vitiate the results of the various tests Indeed circulating anticoagulants are a frequent accompaniment of hemophilia and should be sought in every case

The bleeding time is nearly always normal in hemophilia if it is prolonged the true diagnosis may be vascular hemophilia (Chapter XVII) The tourniquet test usually gives a normal result although it has been reported to be transiently positive during bleeding episodes

It cannot be too strongly emphasized that the diagnosis of hemophilia is not ruled out by obtaining normal results in many tests in current use Whenever discrepancy exists between the patient s history and the results of laboratory tests credence must be given to the story until more subtle tests have been performed Each year we see one or more patients who have bled

lized and cooled by the application of ice bags Hematomas are ordinarily best left untreated Exceptionally, bleeding into a closed space such as the axilla the popliteal space the palmar fascia or the carpal tunnel may threaten to compress major nerves or blood vessels, or tissues may be so distended that necrosis seems imminent Under these conditions the administration of hyaluronidase as suggested by MacAusland and Gartland (381) may speed the absorption of blood Hyaluronidase should be administered only if the patient is treated simultaneously with plasma If hemorrhage into the soft tissues of the neck threatens to compress the trachea and asphyxiate the patient endotracheal intubation or even tracheotomy may be necessary

To prevent its economically crippling sequelae hemarthrosis must be treated with great energy (317) Unfortunately the physician seldom sees the patient until a day or more after bleeding into the joint has begun The affected joint should be immobilized and surrounded by ice packs and a compression bandage should be applied (162 516) Plaster casts are probably best avoided at this stage If bleeding continues or there is evidence of distension of the articular space the joint is aspirated preferably by an orthopedic surgeon and only after the patient has had blood or plasma transfusions (162) The procedure must be done with the strictest aseptic precautions Repeated aspirations may be necessary As soon as bleeding appears to have stopped the patient is encouraged to move the affected joint within the limits of pain and active exercises are begun under the direction of a physiotherapist Early motion only rarely causes a recurrence of bleeding if the initial therapy with plasma has been adequate Early motion of the joint seems to facilitate absorption of blood and to minimize permanent damage

In children who have bled into the knee traction is applied to the lower leg after aspiration in order to minimize contraction deformity Although the hemophiliac may be encouraged to walk on crutches when bleeding has stopped he must not bear weight on the affected joint until he regains good muscular control Sometimes the orthopedist may feel the necessity to protect the joint for a longer period of time by the use of a long leg brace equipped with a knee lock

cross matching individuals who may have had many previous blood transfusions Moreover, if external blood loss is not extensive, repeated transfusions of whole blood increase the iron stores of the body, with possibly deleterious results For these reasons, the transfusion of citrated plasma is preferable Since antihemophilic factor is unstable upon storage at 4°C either freshly prepared citrated plasma or plasma frozen while still fresh, is used (293, 21) Where fresh or freshly frozen plasma is not available commercially lyophilized freshly frozen plasma marketed by Hyland Laboratories, Los Angeles, California is helpful its titer of antihemophilic factor is said to be about half that of unlyophilized plasma (22) Injections of plasma must be repeated at frequent intervals since antihemophilic factor has a biological half life of only a few hours (21)

Depending upon the severity of the bleeding treatment in an adult consists of an intravenous injection of 500 to 1 000 ml of plasma followed by 100 ml every three to four hours until bleeding stops and then by decreasing amounts of plasma over the next few days (534) The larger amounts are given for more alarming bleeding and even more may be necessary if these doses are ineffective Proportionate doses are given to children I aim at an initial level of 20 per cent of the antihemophilic factor titer of normal plasma As my experience has increased I have tended to give larger doses even though I am most sensitive to the possibility of inducing homologous serum jaundice by this procedure There is no easy way to measure the effectiveness of plasma by laboratory tests The clotting time of venous blood is shortened to normal levels by amounts of plasma far less than are needed for hemostasis More elaborate assays such as the thromboplastin generation test or partial thromboplastin time, are impractical in the emergent care of bleeding

Repeated attempts have been made to concentrate antihemophilic factor of human or animal origin (67) Porcine plasma is a particularly rich source of the substance Although recent experience is hopeful human or animal preparations practical for clinical use are not at present available

The third problem in the management of acute bleeding is the prevention of local damage The affected part should be immobi-

cumstances the physician may proceed with surgery over the patient s protests In at least one case with which I am familiar the patient died of resulting hemorrhage As Diamond (166) has recently re emphasized it is the patient s story which should be believed rather than the laboratory tests

Although extraction of carious teeth is a major problem in the management of hemophilia and other bleeding disorders there is no well defined approach to this procedure In general the recommendations of Biggs and Macfarlane (71) form an excellent guide The patient is admitted to the hospital The teeth should be removed with as little trauma as possible Except under un usual circumstances no more than two or three teeth should be removed at a time Extraction is usually best performed under general anesthesia Nasal endotracheal intubation is essential to prevent respiratory difficulty but this procedure should be per formed with gentleness to prevent such complications as epistaxis After the tooth has been removed a light plug of absorbable material such as fibrin foam soaked in thrombin is laid over the socket and held in place by the dentist s finger for several minutes Then a previously prepared dental splint is applied to hold the dressing in place The function of the splint is not to press the dressing into the wound but to protect the area from movements of the tongue and from oral fluids and food Indeed it is impor tant to avoid tight plugging of the socket so that necrosis will not occur The gum margins are not sutured because a hematoma might form which could spread to the pharynx and result in asphyxia The dental dressing may have to be replaced at frequent intervals

Biggs and Macfarlane (71) do not transfuse their patients unless alarming bleeding occurs I follow this practice in mild bleeders In severe hemophilia the patient is prepared as for any surgical procedure by the administration of 1 000 ml of freshly frozen plasma Then about 100 ml of plasma are transfused every three or four hours for as long as a week If oozing occurs at the site of the extraction thrombin is applied locally as a hemostatic agent Often the patient has little or no difficulty until five or six days after extraction when brisk hemorrhage may suddenly ensue Bleeding may then be controlled by local treat

If more persistent deformities such as flexion contracture are present, an attempt is made to correct these, using wedging plaster casts Muscular contractures are treated in the same way Corrective operations are occasionally performed in patients in whom hemophilia can be controlled by transfusion For example de Palma and Cotler (162) have performed arthrodesis at the knee and hip and Dr Paul Curtiss at University Hospitals of Cleveland, has lengthened the scarred and shortened Achilles tendon in three young hemophiliacs In two, complete function was restored to the ankle and in the other a partial correction was achieved One need not point out that such surgery can only be performed under the careful supervision of someone familiar with the treatment of hemorrhagic disease At best continued annoying oozing complicates the postoperative period

The problem of surgery may face the hemophiliac as urgently as any other patient (623) Many surgical procedures have been performed sometimes successfully but frequently with tragic results (127) The indications for surgery in the hemophiliac are often confused For example right lower quadrant pain and tenderness may be due to a retroperitoneal hematoma rather than to acute appendicitis, this was the case in one patient studied at the Cleveland Metropolitan General Hospital Once it is decided that an operation must be performed the patient should be prepared by the transfusion of blood plasma or both so that adequate levels of antihemophilic factor are present prior to the initial incision A typical regimen is the transfusion of a liter of freshly frozen plasma just before the start of the procedure followed by 100 to 200 ml of plasma per hour during surgery and at least 100 ml every three hours for the first twenty four hours The dose of plasma is then gradually decreased during the next week (534 168) I have had no experience with surgery in a patient with a circulating anticoagulant but I fear the result would be disastrous for such patients do not respond to the transfusion of normal plasma

The real danger of surgery is not in the severe hemophiliac but in the mild bleeder who goes to a physician unfamiliar with his case In mild hemophilia tests for hemostatic function may yield normal values in so called routine tests Under such cir

language understandable to a lay person so that proper care can be administered in the event of injury

Hemophiliacs and their families are of course tremendously interested in the genetic risks inherent in the disease One may point out to the patient that his grandsons will be the first of his descendants to have difficulty In substance this means that it may be forty or sixty years before hemophilia will appear in his descendants and a reasonable hope exists that our methods of therapy will have improved by that time The carrier or potential carrier should be instructed in the statistical risks which she faces but I believe that the decision as to whether or not she wishes to have children should be made by her and not by the physician

THE PROGNOSIS OF HEMOPHILIA

The prognosis of hemophilia in patients treated by current techniques is not known Birch (74) in 1937 estimated that 35 per cent of 113 hemophiliacs died within their first year of life 57 per cent within the first five years and 95 per cent by the age of forty However, hemophilia was not clearly differentiated from other coagulative abnormalities at the time of her study and milder cases were overlooked The prognosis of hemophilia is undoubtedly much less gloomy than Birch reported not only because of these differences but because of the availability of blood and plasma to tide patients over crises One Cleveland patient who has moderately severe hemophilia is alive and otherwise healthy at seventy-one years of age and Didisheim and Lewis (168) have described a patient who died at seventy nine

The hemophiliac may not survive the injuries acquired at birth (432) Rarely he may exsanguinate after an injury or surgery or he may bleed into a vital area perhaps strangling from hemorrhage into the soft tissues of the neck or mediastinum Bleeding into the central nervous system once an uncommon cause of death has become more important as other forms of hemorrhage have come under control The patient may succumb to infection within an area made necrotic by the presence of a hematoma One of our patients depressed by his disease committed suicide Finally the patient may survive the risks of hemophilia only to die in the course of events from some other

ment or, if this fails therapy with plasma must be instituted or intensified

The hemophiliac can avoid hemorrhage only to the limited extent that he can avoid injury or operations for nearly all episodes of bleeding seem to begin without obvious trauma The parents of a child with hemophilia should be reassured that each bleeding episode is not due to their carelessness Every effort must be made to curb them from constricting the hemophiliac s mental and emotional development while they guard him from physical injury This is a tight rope which is the harder to walk the more severe the disease The infant is kept in a crib lined with *soft material such as mattress padding and surrounded by* deep carpeting to cushion any falls Lowering the height of the conventional crib will shorten the distance to the floor The child s playpen is similarly padded Toys with sharp edges and dangerous points should be avoided but this is advice applicable to any child A severe hemophilic toddler may wear a football helmet to protect him against hematomas of the scalp a common *injury* Tricycle peddles should be carefully padded As the child grows older he should avoid body contact sports but swimming golfing and sailing are reasonably safe One may point out to him that these are sports which anyone can pursue in middle life The child should be trained for a sedentary occupation It may help to overcome his feeling of hopelessness about the future to realize that hemophiliacs have become successful teachers musicians engineers physicians draftsmen research chemists and merchants

Considerable practical help in orienting patients and their families may be obtained from the Hemophilia Foundation whose national offices are at 175 Fifth Avenue New York 10 New York They have prepared a pamphlet dealing with the home care of the hemophiliac especially suitable for lay instruction (709) Chapters of the Hemophilia Foundation exist in many cities similar societies function in several European countries

Although the transfusion of blood or plasma at frequent intervals has been recommended as a prophylactic measure (30), I do not believe that this procedure *is practicable* At the same time it carries with it the danger of homologous serum jaundice and possibly of the development of a circulating anticoagulant Every bleeder should carry a note which gives the diagnosis in

Until recently the rarity of hemophilia in the female was attributed to the possibility that the homozygous state for the abnormal gene was lethal for the embryo However in canine hemophilia the mating of an affected male and a carrier female does result in the birth of hemophilic females (94) At least four authentic cases of hemophilia in the human female have now been reported (300 429) These hemophiliacs were the offspring of marriages between hemophiliacs and carriers (Figure 2) The female hemophiliacs have had the usual symptoms of the disease and in addition menorrhagia Although she survived childbirth one patient had intractable uterine hemorrhage ten days after delivery controlled only by hysterectomy Hemophilia in the female must be distinguished from the carrier state in which hemorrhagic symptoms are occasionally present and the titer of circulating antihemophilic factor may be abnormally low (393 480a) It may also be confused with vascular hemophilia a hemorrhagic disorder of both sexes in which the laboratory abnormalities include both a low titer of antihemophilic factor and a prolonged bleeding time (Chapter XVII) In one interesting case study of the chromosomes of a "female" hemophiliac showed that she was genetically male despite her physical make-up (363)

SELECTED REFERENCES

15 Aggeler P M Treatment of hemophilia *Blood 11* 81 1956

22 Alexander B Coagulation hemorrhage and thrombosis *New Eng J Med* 252 432 484 526 1955

74 Birch, C LaF Hemophilia—Clinical and genetic aspects *Illinois Medical and Dental Monographs* Urbana U of Illinois Press I No 4 1935-1937

149 Davidson C S Hemophilia Clinical study of 40 patients *Blood* 4 97 1949

243 Graham J B Biochemical genetics of blood coagulation *Am J Human Genet* 8 63 1956

317 Jordan H H *Hemophilic Arthropathies* Springfield Charles C Thomas 1958

391 Macfarlane R G and Biggs R The diagnosis and treatment of hemophilia and related conditions *Medical Research Council Memorandum No* 32 London H M Stationery office 1955

623 Spaet, T Recent progress in the study of hemophilia, *Stanford M Bull* 13 24 1955

illness, one patient under my care died at sixty three years of age of carcinoma of the stomach

THE CARRIER STATE IN HEMOPHILIA

As has been said, the female carriers of hemophilia are nearly always asymptomatic From the point of view of eugenics, it is of value to detect these female carriers Three groups of in dividuals may be identified as carriers on the basis of genetic theory namely, all daughters of hemophiliacs the mother of two or more hemophiliacs or the mother of one hemophiliac when she has other hemophilic relatives

Attempts to identify other carriers on the basis of history or laboratory examination have had only limited success Although some carriers may give a history of mild bleeding they are much more likely to be aware of bleeding symptoms than persons with out hemophilic relatives Nonetheless in a few families females describe such phenomena as epistaxes ecchymoses and menor rhagia More usually the females are asymptomatic

Many attempts have been made to recognize the carrier state in the laboratory (409) In most studies antihemophilic factor was not measured specifically so that any abnormality detected may have been due to irrelevant changes On the other hand the great variation in normal plasmas must be taken into account (633 498) In several careful studies a number of carriers have had partial but significant deficiencies of antihemophilic factor (167 498 409a) Usually these identifiable carriers are related to patients with mild hemophilia (247 409) but this is not an in variable rule (167) The proportion of carriers with abnormally low titers of antihemophilic factor has varied from series to series depending to some extent upon the sensitivity of the methods used Within a given family the concentration of anti hemophilic factor varies unpredictably from carrier to carrier (534 393) The genetic explanation for differences among carriers within a single family is not clear

HEMOPHILIA IN THE FEMALE

Genetically the union of a hemophilic male and a female carrier should result in hemophilic females in one fourth of births

was the cause of death in the only fatal case in my own experience The extraction of teeth tonsillectomy and other operative procedures are accompanied by severe hemorrhage controlled only with the greatest difficulty In two instances traumatic rupture of the spleen has complicated the disease (534)

The severity of Christmas disease varies from family to family (521) mild Christmas disease is probably relatively more common than mild classic hemophilia (71) Several of Quick s patients thought that bleeding was more frequent at times when they were ingesting aspirin (521) In general however, one cannot distinguish Christmas disease from hemophilia without laboratory studies

Classic hemophilia is reported to be about five times as common as Christmas disease (168 542) The true incidence of Christmas disease is probably less than this In our own experience 81 per cent of sixty three families have had hemophilia and 19 per cent Christmas disease However only 11 per cent of forty seven families residing in the metropolitan area of Cleveland have had Christmas disease Thus it is possible that Christmas disease is rarer than has been assumed and that some undefined influences have led patients with this disease to the specialized laboratory for diagnosis

The fundamental defect in Christmas disease appears to be a failure to synthesize Christmas factor This factor associated with the beta globulins is present in both normal plasma and serum In common with prothrombin pro SPCA and Stuart factor it can be adsorbed from plasma by such substances as barium sulfate and aluminum hydroxide from which it can then be eluted and partially purified (17) The site of synthesis of Christmas factor is unknown but it may be pertinent that the concentration of Christmas factor is depressed in the plasma of some patients with hepatic disease (533) The concentration of Christmas factor is depressed in patients treated with coumarin like drugs (70) the administration of Vitamin K_1 corrects drug induced deficiency of Christmas factor

Christmas factor seems to serve an important role in the development of thromboplastic activity in shed blood but its actual function is unknown Fragmentary evidence suggests that it may

Chapter IV

CHRISTMAS DISEASE

UNTIL recently, hemophilia was assumed to be a single entity With the development of modern techniques this concept became untenable as evidence accrued that more than one biochemical lesion might be associated with the identical clinical syndrome In 1947, Pavlovsky (480) reported that a mixture of the blood of two hemophiliacs clotted more rapidly than either blood alone an observation soon confirmed by Koller (334) Then, in 1952 three separate groups of investigators (576 17, 70), noting the same paradox, divided patients with clinical hemophilia into two groups those whose plasma was deficient in classic antihemophilic factor and those lacking a second substance variously called Christmas factor plasma thromboplastin component (PTC) antihemophilic factor B factor IX or beta prothromboplastin Patients deficient in Christmas factor are said to have Christmas disease or PTC deficiency

Clinically Christmas disease is virtually indistinguishable from classic hemophilia It is a life long disorder primarily of males transmitted as a sex linked recessive trait (Figure 2) (443) In most patients, a family history of bleeding can be elicited (168) The female carriers are usually asymptomatic though a substantial number have a mild bleeding tendency (167, 72, 365) Christmas disease has been reported from laboratories all over the world no racial group seems particularly susceptible

To recite the symptoms of Christmas disease is to repeat monotonously the description of classic hemophilia Patients with Christmas disease bleed into their skin soft tissues and joints either spontaneously or after minor injuries Bleeding from the mucosal surfaces and hematuria are common As in hemophilia a patient occasionally bleeds into the central nervous system this

was the cause of death in the only fatal case in my own experience The extraction of teeth tonsillectomy and other operative procedures are accompanied by severe hemorrhage controlled only with the greatest difficulty In two instances traumatic rupture of the spleen has complicated the disease (534)

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Christmas factor seems to serve an important role in the development of thromboplastic activity in shed blood but its actual function is unknown Fragmentary evidence suggests that it may

become activated in the presence of Hageman factor, plasma thromboplastin antecedent and calcium ions It then may react in an unexplained way with antihemophilic factor, at which stage of this reaction the platelets participate is unknown Ultimately, thromboplastic activity, equivalent in its effect to tissue thrombo plastin, appears and institutes the formation of thrombin Unlike antihemophilic factor, Christmas factor does not disappear during the clotting process

The diagnosis of Christmas disease is made in the laboratory The platelet count bleeding time and tourniquet test have almost invariably been normal The clotting time of whole blood in glass tubes is often prolonged but in mild cases may be normal (168) On the other hand, the clotting time in silicone coated or Lusteroid tubes is nearly always prolonged As in classic hemophilia the defect appears to be localized to the earliest stages of clotting the thrombin time and the prothrombin time are normal Serum prothrombic activity is usually abnormally high indicating defective conversion of prothrombin to thrombin but if the disease is mild the results of this test may be normal. The results of the thromboplastin generation test are usually abnormal The defect measured in this test is corrected by normal serum but not by normal aluminum hydroxide adsorbed plasma, a reagent which is deficient in Christmas factor The diagnosis rests ultimately upon demonstrating that the plasma of a patient known to have Christmas disease does not correct the defect in the plasma under study As in the case of hemophilia various techniques may be used to perform this cross matching If plasma from a recognized case is not available a presumptive diagnosis can be entertained if the abnormality in the patient s plasma is corrected by normal serum but not by normal adsorbed plasma

The degree of the defect measurable in the laboratory varies from family to family the concentration of Christmas factor in the patient s plasma seems inversely proportional to the severity of the disease Similarly the concentration of Christmas factor in the plasma of some of the female carriers of the trait may be lower than that of normal plasma (72 564 167)

An impression exists that the prognosis of Christmas disease is better than that of hemophilia (168 521) but sufficient data to

establish this point have not yet accumulated The treatment of Christmas disease is essentially the same as that of hemophilia the discussion of this problem in Chapter III should be consulted However Christmas factor is more stable than antihemophilic factor so that blood which has been stored in a blood bank for several weeks can be transfused with advantage (564) When bleeding is not associated with a fall in hematocrit fresh or frozen plasma can be used The amount of blood or plasma needed seems to be less than that required for the treatment of hemophilia (662) as one would expect since the defect in Christmas disease may be corrected for forty eight hours or longer by the transfusion of a single unit of blood or plasma (18) Concentrates of Christmas factor suitable for therapy are not yet generally available although progress in this direction has been made (169) The prophylactic use of repeated transfusions of plasma has been recommended for the care of patients with severe Christmas disease but as in classic hemophilia this practice is attended with the risks of homologous serum jaundice and perhaps of the development of circulating anticoagulants

Resistance to the beneficial effects of transfusion and the presence of circulating anticoagulants (616 364) have been described in a few cases of Christmas disease Therapy in such cases is difficult because the Christmas factor in transfused blood is inactivated by the anticoagulant This problem is discussed in greater detail in Chapter XI

SELECTED REFERENCES

18 Aggeler P M White S G and Spaet T H Deuterohemophilia Plasma thromboplastin component (PTC) deficiency Christmas disease hemophilia B *Blood* 9 246 1954

22 Alexander B Coagulation hemorrhage and thrombosis *New Eng J Med* 252 432 484 526 1955

443 Moor Jankowski J K Huser H J Rosin S Truog G Schneeberger M and Geiger M *Hemophilia B Genetics Hematology and Clinical Aspects* Basel S Karger 1958

521 Quick A J and Hussey C V Hemophilia B (PTC deficiency or Christmas disease) *A M.A Arch Int Med* 103 762 1959

Chapter V

HAGEMAN TRAIT

THE value of genetic abnormalities in clarifying normal physiology is no more clearly exemplified than in the strange syndrome Hageman trait (537) In this disorder the clotting time of venous blood is greatly prolonged, to the degree usually associated with severe bleeding Surprisingly patients with Hageman trait have little or no evidence of a bleeding tendency The prolonged clotting time is related to a deficiency of a specific clot promoting substance Hageman factor Hageman factor is necessary for clotting to proceed at a normal rate in the test tube, yet its absence does not seem to hamper patients with Hageman trait in a detectable way

No studies are available concerning the frequency of Hageman trait Presumably it is a rare disorder About thirty five cases equally divided between the sexes, have been identified with certainty In one patient blood transfusions were needed after the delivery of each child and some bleeding followed dental extractions (73) In two others frequent epistaxes and easy bruising were noted (618) None of the other patients with Hageman trait has had abnormal bleeding despite the ordinary dental extractions operative procedures deliveries and injuries one would expect in any group of people

Hageman trait is probably a life long disorder in two cases the prolonged clotting time was recognized many years before the diagnosis was established The defect is evidently inherited In one family the abnormality was recognized in two sisters (537) and in another in a brother and sister (543) The family tree of the two sisters suggested that Hageman trait results from the inheritance of abnormal recessive genes for they descended from a consanguineous union (409) Data obtained in other families

support this view (381a) The clotting time of blood obtained from the parents or offspring of affected individuals has invariably been normal However the parents of individuals with Hageman trait sometimes have a partial deficiency of Hageman factor revealed by more subtle tests (536, 102)

The defect in Hageman trait resides in the earliest part of the clotting process Besides the prolonged clotting time studies consistently show impaired prothrombin "consumption" and "thromboplastin generation The platelet count prothrombin time and thrombin time are normal The abnormality in clotting can be corrected by the addition of very small amounts of plasma or serum obtained from normal individuals or from patients with other known coagulative defects A positive diagnosis can be made by observing that the patient s plasma does not correct the coagulative defect of plasma obtained from a patient known to have Hageman trait Suitable control experiments must be performed to rule out the presence of a circulating anticoagulant

The abnormality in the plasma of patients with Hageman trait can be corrected by the addition of a fraction of normal plasma freed from all other known clotting factors (537) A similar fraction prepared from the plasma of patients with Hageman trait is without effect The corrective fraction is present in the plasma of rats rabbits dogs sheep mice guinea pigs opossums and horses On the other hand the plasma of ducks and chickens lacks this activity At first it was thought that the fraction prepared from normal plasma or serum which corrects the defect in Mr Hageman s plasma could be equated with Hageman factor the substance lacking in Hageman s plasma More recently evidence has appeared from several laboratories suggesting a more complicated state of affairs (536 621 260 535 684)

One of the major mysteries concerning clotting has been that blood which clots so readily in glass tubes remains fluid in the circulation Bordet (86) long ago demonstrated that glass reacts with some component of plasma to initiate clotting Which of the clotting factors was affected by contact with glass has been disputed Recently Shafrir and de Vries (589) and Margolis (411) demonstrated that the action of glass was mediated

through a substance in plasma resembling either Hageman factor or plasma thromboplastin antecedent Subsequent to their reports several investigators demonstrated that the substance which was activated by glass was identical with Hageman factor (546 73, 621, 685) The manner in which glass reacts with Hageman factor is not certain Glass is a highly adsorptive substance clotting is accelerated when blood comes in contact with a number of other adsorbents, including kaolin, bentonite barium carbonate supercel and silicic acid Indirect evidence has been obtained that glass activates Hageman factor by removing an inhibitor (546) this reaction seems to take place at the surface of the glass (684, 260) The Hageman factor, thus freed from inhibition then initiates clotting Several lines of experimentation lead to the conclusion that Hageman factor then reacts with plasma thromboplastin antecedent to produce a clot promoting substance (536 260 535 684) this clot promoting substance is probably identical with the fraction of normal plasma which corrects the defect in the plasma of patients with Hageman trait Hageman factor itself has been prepared free of other clotting factors by using plasma deficient in plasma thromboplastin antecedent as the starting material (535) The clot promoting substance which evolves from Hageman factor and plasma thromboplastin antecedent can be purified many times human serum contains no more than 2 mg per liter (535) How the clot promoting substance then works is unclear Becker (49) believes that it may act as an enzyme but whether its substrate is Christmas factor antihemophilic factor or some other factor is not known

Plasma also contains a factor which seems to inactivate the clot promoting substances which evolves from the action of Hageman factor (412 546) This inactivator destroys the clot promoting substance by what may be an enzymatic process Teleologic reasoning suggests that this inactivator may be important to prevent the formation or extension of intravascular thrombi

Whether Hageman factor plays any other biological role is uncertain Margolis believes that it may be needed for the evolution of substances in serum which stimulate smooth muscle

(413) and increase capillary permeability (414) One wonders whether Hageman factor is an enzyme which working upon several substrates in the blood may be responsible for a variety of physiologic effects

Finally the reader will note that no explanation is forthcoming for the paucity of hemorrhagic symptoms in patients lacking Hageman factor Our failure to understand this strange phenomenon underlines the primitive nature of our concepts of hemostasis

SELECTED REFERENCES

260 Hardisty R M and Margolis J The role of Hageman factor in the initiation of blood coagulation *Brit J Haemat* *5* 203 1959

413 Margolis J Activation of plasma by contact with glass Evidence for a common reaction which releases plasma kinin and initiates coagulation *J Physiol* *144* 1 1958

537 Ratnoff O D and Colopy J E Familial hemorrhagic trait associated with deficiency of clot promoting fraction of plasma *J Clin Invest* *34* 602 1955

546 Ratnoff O D and Rosenblum J M Role of Hageman factor in the initiation of clotting by glass *Am J Med* *25* 160 1958

Chapter VI

DEFICIENCY OF PLASMA THROMBOPLASTIN ANTECEDENT

IN 1953 Rosenthal Dreskin and Rosenthal (568) described a new syndrome whose puzzling nature has served as an important stimulus for research into the nature of the clotting process Named plasma thromboplastin antecedent (or PTA) deficiency, the less committal term Rosenthal's syndrome, suggested by Biggs (73), has much to commend it until the true mechanisms underlying the disease are appreciated

In a recent review Rosenthal (567) summarized the evolution of the concept of PTA deficiency Patients with PTA deficiency bleed excessively after surgical procedures particularly tonsillectomy and dental extractions and injuries Epistaxes are common but other forms of spontaneous bleeding are unusual and hematomas and hemarthroses are distinctly rare Menorrhagia is infrequent, but may be severe enough to lead to hysterectomy (73) Occasionally easy bruising is noted Spontaneous cerebral hemorrhage (280) and bleeding *post partum* (526) have been described

PTA deficiency occurs about twice as often in females as in males and is apparently a familial disorder Its mode of inheritance is disputed (567, 103), but a simple dominant pattern with incomplete transmission has been observed in a number of cases The possibility has been suggested that a disproportionately large proportion of the patients are Jewish (73) Although cases similar to those described by Rosenthal have been studied in many laboratories there is a great variation in its recorded frequency in different areas For example Rosenthal observed as many cases of this disorder as of classic hemophilia (567) yet Biggs and her

associates found only three cases compared to 139 families with classic hemophilia (73), and I am unaware of an authentic case in Cleveland

The chief abnormalities noted in the laboratory are found in the tests for prothrombin "consumption" in clotted blood and for "thromboplastin generation In mild cases diminished prothrombin "consumption" may be the only defect noted The addition of small amounts of plasma or serum from normal individuals or from patients with other hemorrhagic disorders corrects this abnormality An important exception to this generalization is that plasma from patients with Hageman trait may be less effective than normal plasma (223)

In more severe cases the thromboplastin generation test is abnormal The defect can be corrected by the substitution of normal aluminum hydroxide adsorbed plasma or normal serum differentiating PTA deficiency from hemophilia and Christmas disease respectively Hageman trait and PTA deficiency can be distinguished by taking advantage of the fact that plasmas obtained from patients with each disorder are mutually corrective in appropriate test systems Only occasionally is the clotting time of whole blood or of recalcified plasma prolonged or the tourniquet test or bleeding time abnormal The prothrombin time is invariably normal the defect seems localized to the early phases of clotting

Ultimately the diagnosis of PTA deficiency rests upon demonstrating that the defect in the blood under study is not corrected by the blood or plasma of Dr Rosenthal s original patient and *vice versa* By this technique, Biggs and her associates (73) and Soulier (618) were able to establish the diagnosis in patients under their care This criterion has not always been met in the published studies about this disease A major handicap has been the lability of the defect the plasma of most patients with PTA deficiency behaves like normal plasma after it has been stored for several days either in a refrigerator or freezer (566) As a result uncertainty exists that all of the cases reported in the literature as instances of PTA deficiency actually are examples of one and the same disorder (71)

The nature of the defect in PTA deficiency is yet to be satis

factorily explained The viewpoint most consistent with the published data is that patients with this disease lack a specific clotting factor, plasma thromboplastin antecedent Supporting this view is the observation that a fraction of normal plasma corrects the defect in the plasma of patients with PTA deficiency A similar fraction prepared from the patient with PTA deficiency, seems to lack activity attributable to this clotting factor (535)

The possibility must be entertained that in certain of the cases which have been diagnosed as PTA deficiency, the syndrome is due instead to the presence of a weak circulating anticoagulant For example, Rosenthal (567) pointed out that the plasma of a patient with severe PTA deficiency inhibits prothrombin consumption in normal blood and Lisker and his associates (369) using a technique not previously applied to such cases, demonstrated a circulating anticoagulant in a patient thought to be PTA deficient The lability of the defect in this disorder, mentioned previously might reflect the lability of this anticoagulant

The function of plasma thromboplastin antecedent is unknown but evidence reviewed on page 54 indicates that it reacts with Hageman factor to form a clot promoting substance Experiments of Margolis suggest that plasma thromboplastin antecedent may be consumed when blood is exposed to glass under appropriate conditions (413)

Fortunately bleeding in plasma thromboplastin antecedent only rarely threatens life although fatal cases have been described The only treatment that has been evaluated to date has been the transfusion of normal blood or plasma This therapy has been of limited value transfusion of 450 ml of plasma has been without significant effect on tests of hemostatic function though it is said to prevent bleeding during surgery One might speculate about the use of normal plasma freshly treated with glass, but this method of treatment has not yet been attempted

SELECTED REFERENCES

526 Ramot B Angelopoulos B and Singer K Plasma thromboplastin antecedent deficiency *A M A Arch Int Med* 95 705 1955

567 Rosenthal R L *The Present Status of Plasma Thromboplastin Antecedent (PTA) Deficiency in Hemophilia and Hemophilioid*

Diseases K. Brinkhous Edit Chapel Hill, U of N Carolina Press 1957
568 Rosenthal R L Dreskin O H and Rosenthal N New hemophilia like disease caused by deficiency of third plasma thromboplastin factor *Proc Soc Exper Biol & Med* 82 171 1953

Chapter VII

THE VITAMIN K-DEPENDENT CLOTTING FACTORS

FOUR of the recognized clotting factors in human plasma prothrombin pro SPCA Stuart factor and Christmas factor have remarkably similar properties All require Vitamin K for their synthesis which is consequently inhibited by anything diminishing the supply absorption or utilization of this substance All are stable upon storage at 4°C in citrated or oxalated plasma and except for prothrombin all are present in the serum after coagulation has apparently been completed All are adsorbed from plasma by such substances as barium sulfate calcium phos phate or aluminum hydroxide and can then be eluted from these adsorbents And all are readily inactivated by compounds contain ing sulfhydryl groups

Among these four Vitamin K dependent factors the chemistry and function of prothrombin is most clearly defined Prothrombin is a plasma protein which in the purified state is usually resistant to heat and acid (71) It can be readily separated from other Vitamin K dependent clotting factors by column chromatography (150) During clotting prothrombin is converted to a molecule half its size thrombin a hydrolytic enzyme which partially di gests fibrinogen with the ultimate result that a fibrin clot forms The conversion of prothrombin to thrombin is accomplished by *the successive interactions of thromboplastin originating from* plasma or tissue proaccelerin pro SPCA Stuart factor and cal cium Highly purified preparations of prothrombin can also be activated to thrombin by concentrated solutions of sodium citrate (583), but this activation too may require the presence of ad ditional clotting factors (23 647)

Pro SPCA and Stuart factor have been differentiated by the

study of patients who have hereditary deficiencies of one or the other of these proteins, but only imperfect separations have been accomplished by chemical means (150) Both pro-SPCA and Stuart factor seem necessary for the action of *tissue* thromboplastin upon prothrombin, evidence that only Stuart factor is needed for the action of thromboplastin of plasma origin is summarized on page 73 How these two substances execute their effects is entirely unknown at this time The fourth Vitamin K-dependent clotting factor Christmas factor or plasma thromboplastin component has been discussed in Chapter IV Although Christmas factor is clearly implicated in the development of thromboplastic activity in plasma its chemistry and function are a mystery

The four Vitamin K-dependent clotting factors behave in a similar fashion during health and disease Their concentration is low at birth and may decrease even further during the first few days of life resulting in hemorrhagic disease of the newly born During normal pregnancy on the other hand the concentration of all four factors is elevated In patients with hepatic disease or in those in whom absorption of fats from the intestinal tract is impaired the concentration of all may be depressed These similarities remain unexplained Lasch and Roka (349) and Alkjaersig and Seegers (34) have championed the view that these clotting factors are chemically related to each other and can be converted one to another The experimental basis for this appealing view is not yet adequate

Knowledge of the role of Vitamin K in blood coagulation stems from the pioneer studies of Dam and his associates who demonstrated that chicks fed certain synthetic diets developed a bleeding tendency (137) The hemorrhagic symptoms could be prevented by the administration of a substance present in cereals which they named Vitamin K (139) Quick (511) and Dam Schønheyder and Tage Hansen (140) then demonstrated independently that the bleeding tendency in the deficient chicks was related to a deficiency of prothrombin in their plasma Quick observed that the concentration of prothrombin could be restored by the administration of alfalfa a rich source of Vitamin K

At about the same time evidence appeared that the synthesis

of prothrombin depends upon the integrity of the liver Warner, Brinkhous and Smith (610, 695) confirmed earlier observations that such hepatotoxins as phosphorus and chloroform cause a decrease in the concentration of prothrombin in canine blood, they concluded that prothrombin is synthesized in the liver, an interpretation corroborated by Quick's (512) similar studies Moreover, the concentration of prothrombin fell after partial or total hepatectomy These experiments suggested that the liver is either the site of synthesis of prothrombin or a site for some step in the synthetic process Similar experiments have implicated the liver in the synthesis of pro SPCA (405) Direct evidence of the production of prothrombin and of pro SPCA by isolated liver slices has been published recently by Pool (501)

In 1935, Hawkins and Whipple (276) observed that dogs in which bile is diverted from the intestinal tract develop a bleeding tendency This hemorrhagic state is accompanied by a deficiency of prothrombin (275) When it was found that Vitamin K corrects hypoprothrombinemia in deficient chicks Greaves and Schmidt (251) and Smith and his associates (611) showed that this vitamin also corrects the prothrombin deficiency in animals with bile fistulas Presumably bile salts are needed for the absorption of Vitamin K from the intestinal tract

In agreement Quick Stanley Brown and Bancroft (523) reported that the prothrombin time is often prolonged in obstructive jaundice The presence of hypoprothrombinemia in such cases was confirmed by Brinkhous, Smith and Warner (96) and others The prolonged prothrombin time can be shortened by the oral administration of Vitamin K (696) As might be anticipated the simultaneous administration of bile salts facilitates the absorption of the vitamin

From these observations the unifying concept arose that Vitamin K is absorbed from the gastrointestinal tract only in the presence of bile salts and is then utilized by the body for the synthesis of prothrombin Vitamin K is also needed for the synthesis of Christmas factor pro SPCA and Stuart factor How Vitamin K is utilized in these syntheses is not understood It is not incorporated into the molecule of prothrombin nor in all likelihood, into the other Vitamin K dependent clotting factors Experimentally Vitamin K functions as a co enzyme for electron

transport and coupled oxidative phosphorylation (421, 174 722 125) but how these functions influence the synthesis of the four clotting factors is not understood Indeed it is not known whether Vitamin K is needed for the formation of other proteins which are not so readily identified as these clotting factors

It was soon apparent that a prolonged prothrombin time was found not only in cases of obstructive jaundice but also in intra hepatic disease particularly cirrhosis of the liver or severe acute hepatitis Scanlon and his associates (573) showed that an abnor mally low concentration of prothrombin was present in such cases More recently it has been demonstrated that deficiencies of proaccelerin (269 265) and of the other Vitamin K-dependent clotting factors Christmas factor (448 209) pro SPCA (25) and probably Stuart factor occur with considerable frequency in patients with hepatic disease Deficiencies of any of these substances with the exception of Chrismas factor also result in prolongation of the one stage prothrombin time However in patients with parenchymal hepatic disease the administration of Vitamin K does not restore the prothrombin time to normal (573) Olwin (469) and Lord and Andrus (377) used this difference in response to Vitamin K in the differential diagnosis of jaundice In patients with obstructive jaundice the parenteral administration of as little as 2 mg of menadione results in a significant shortening of the one stage prothrombin time within forty eight hours Indeed if one uses Vitamin K_1 an appreciable decrease in the prothrombin time may be noted within a few hours On the other hand in patients with parenchymal hepatic disease the adminis tration of Vitamin K does not shorten the prothrombin time This test is of the greatest value in the differential diagnosis of jaun dice However one should measure the prothrombin time at least twice before the administration of Vitamin K to avoid misinter pretation based upon laboratory error After the Vitamin K is administered parenterally, the prothrombin time is measured daily to determine whether or not a change will occur Of course a shortening of the prothrombin time indicates only that there may be obstruction to the flow of bile but does not localize the obstruction The further decision remains whether the obstruction is within or without the liver

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Deficiencies of the Vitamin K dependent clotting factors may

contribute to the bleeding tendency of patients with liver disease or obstructive jaundice In patients with obstructive jaundice, bleeding may occur when the prothrombic activity, as measured by the one stage method falls below 20 per cent of normal Quick (513) described gastrointestinal hemorrhage, cutaneous ecchymoses oozing of blood from the mucous membranes hematuria, hemarthroses and occasionally intracranial bleeding Hemorrhage was once a major hazard in the surgical treatment of obstructive jaundice Nowadays the parenteral administration of Vitamin K will usually prevent this potentially lethal accident

Hemorrhagic phenomena and bleeding during surgical procedures are also common in liver disease Deficiencies of many clotting factors may contribute to the hemostatic defect (533) In addition to deficiencies of the Vitamin K dependent clotting factors the patient with liver disease may have partial deficiencies of fibrinogen (209) proaccelerin (269 265), antihemophilic factor (633) and Hageman factor (533) Thrombocytopenia is common particularly in the presence of portal hypertension (565) The coagulability of fibrinogen may be altered (532) Moreover in many patients with chronic hepatic disease clotted blood or plasma lyses more rapidly than normally (240 529) This fibrinolysis is usually too weak to account by itself for hemorrhagic symptoms but possibly it potentiates other hemostatic defects

When patients with liver disease must be operated upon one should have in reserve fresh blood drawn into plastic containers Should transfusions be necessary this blood will contain maximal amounts of the factors likely to be deficient in such patients (209) Special care must be taken in the transfusion of patients with liver disease because they are unable to metabolize citrate used as the anticoagulant as rapidly as normal individuals Rarely the unmetabolized citrate may be responsible for serious or fatal cardiac abnormalities Empirically one gram of calcium gluconate may be administered intravenously after every second blood transfusion to patients receiving more than one transfusion per hour (367)

Most of the Vitamin K absorbed from the gastrointestinal tract is not derived from the diet but is synthesized within the lumen

of the small bowel by bacterial flora As a result, deficiencies of the Vitamin K dependent clotting factors may develop in patients treated with oral chemotherapeutic agents (514) or antibiotics especially the tetracyclines Under such conditions bleeding may appear with dramatic suddenness particularly in infants and children The oral administration of Vitamin K should therefore be considered whenever it is likely that a patient is to be treated with orally administered antibiotics for a protracted period

Deficiencies of the Vitamin K dependent clotting factors may also occur whenever there is malabsorption from the intestinal tract For example in patients with sprue gastro-colic fistulas and other chronic diarrheas the prothrombin time may be prolonged and hemorrhagic symptoms appear unless Vitamin K is given parenterally (624 71 692) Oral Vitamin K in large doses may also be helpful

HEMORRHAGE AS A COMPLICATION OF THERAPY WITH COUMARIN LIKE DRUGS

The story of the development of the use of coumarin compounds to prevent the formation and extension of intravascular thrombi has been reviewed many times and will not be repeated here A number of compounds nearly all structurally similar to Vitamin K appear to depress the formation of those clotting factors which require this vitamin for their synthesis These "anticoagulant substances probably act as competitors for the site of action of the vitamin The resultant impairment of coagulation is reflected by abnormalities detected *in vitro* and if the amount of the drug ingested is sufficiently high by bleeding

Since Vitamin K is needed for the formation of at least four clotting factors—prothrombin pro SPCA Stuart factor and Christmas factor—it is not surprising that the concentration of each of these substances is depressed in patients treated with coumarin like anticoagulants The rate at which the concentration of each clotting factor decreases is thought to vary with the individual drugs used—Dicumarol ethyl biscoumacetate (Tromexan), coumadin (Warfarin) phenylindandione (Hedulin) and so forth (71) The reason that the response is variable is not apparent In addition each patient seems to behave somewhat differently

to the administration of the coumarin like drugs Their action seems to be influenced by many factors such as the presence of hepatic or renal disease, or the coincident administration of salicyl ates, the structure of which is similar to that of Dicumarol As a result the clinical use of these agents is often difficult, and hemorrhage is a common complication of both short and long term anticoagulant therapy (333) For example in a thorough study of anticoagulant therapy in Holland (316), hemorrhagic complications occurred in 7 per cent of cases In a similar study in this country (603) 27 per cent of patients bled excluding cases in which another cause for bleeding was demonstrable

The commonest type of bleeding in patients on anticoagulant therapy is hematuria Blood cells are usually found only upon microscopic examination of the urine but there may be gross hematuria a complication sometimes heralded by aching in the loins (491) Epistaxes, gastrointestinal bleeding ecchymoses, hemoptyses bleeding into the central nervous system bleeding after dental extraction and other bleeding symptoms may occur Severe bleeding is sometimes preceded for a day or two by malaise and lassitude (491) At times these complications may be lethal bleeding into the brain or into the gastrointestinal tract is particularly ominous To prevent the hemorrhagic complica tions of anticoagulant therapy certain precautions should be taken Anticoagulant therapy is contraindicated in patients with injury or recent surgery to the brain or spinal cord joints or genitourinary tract (186) Nor should it be used for patients with subacute bacterial endocarditis or patients with a known bleeding tendency If possible anticoagulant therapy should be avoided in patients with renal or hepatic disease or with ulcera tion of the gastrointestinal tract or elsewhere if the indication for treatment is compelling the drug should be used with great caution

The prothrombin time should be measured at frequent inter vals, at first daily and later, during long term therapy, at least once a week However one should keep in mind that the pro thrombin time does not reflect the full impact of the coumarin like drugs for it does not measure the concentration of Christmas factor whose synthesis is impaired by this therapy (70) In one

study of the complications of anticoagulant therapy seven of twenty three patients who developed a bleeding tendency had a prothrombin time within a supposedly safe range 20 per cent of normal prothrombic activity or higher (603) Unfortunately laboratory aids to circumvent the inadequacies of the one stage prothrombin time are impractical

Since salicylates may augment the effect of the coumarin like drugs their use in patients receiving long term anticoagulant therapy should be discouraged Patients should be instructed to report any suspicious symptoms of bleeding however trivial It is probably wise to examine the urine frequently for microscopic hematuria a warning signal that more serious hemorrhage may occur

The effect of the coumarin like drugs may be reversed by the intravenous administration of 50 to 150 mg of Vitamin K_1 (Mephyton) injected at a rate of no more than 10 mg per minute (549) The concentration of the Vitamin K-dependent clotting factors usually increases to safe levels within four to eight hours Violent bleeding may be treated by the transfusion of fresh or stored blood which usually corrects the coagulative defect promptly Blood transfusion is also useful if surgery must be performed without delay However blood transfusions may not be advisable for many patients treated with anticoagulants In these cases one can usually take advantage of the rapid response to Vitamin K_1

I have mentioned the danger of salicylates in patients treated with coumarin like drugs Large doses of salicylates by themselves may cause a bleeding tendency by depressing the formation of the Vitamin K dependent clotting factors (582) In one 91 year old woman ordinary therapeutic doses of salicylates led to such severe depression of these clotting factors that bleeding ensued (460) The symptoms and laboratory abnormalities were readily corrected by the intravenous injection of Vitamin K_1 Rarely salicylates may also cause bleeding by inducing thrombocytopenia

A severe bleeding tendency apparently due to a deficiency of the stable serum factors has been described in a patient with thyrotoxicosis treated with propylthiouracil (129) The transfusion of normal blood and serum corrected the defect

HEMORRHAGIC DISEASE OF THE NEWBORN

In comparison to adults the hemostatic mechanisms of the newborn human infant are usually grossly abnormal The one stage prothrombin time may be prolonged and the concentrations of prothrombin (95) the stable serum factors, pro SPCA and Stuart factor (68 181 189), Christmas factor (385 1) and probably Hageman factor (384) are usually depressed At birth the concentration of fibrinogen is normal but it may differ qualitatively from adult fibrinogen coagulating more slowly upon the addition of thrombin (68) The clotting time the platelet count and the concentration of proaccelerin are usually normal

During the first few days after birth the concentrations of prothrombin, the stable serum factors and Christmas factor fall to still lower levels and the clotting time may be prolonged (254) For example in one series of breast fed babies the concentration of prothrombin fell to as little as 7 or 8 per cent and that of the stable serum factors to 16 per cent of adult values (189) Within a week after birth the concentrations of these various proteins and of Hageman factor (384) increase without specific therapy

Rarely when the abnormalities of the clotting mechanism are particularly severe they may be accompanied by bleeding resulting in the syndrome called hemorrhagic disease of the newborn Symptoms usually appear precipitously upon the second or third day of life last for two or three days and then if the infant survives disappear with equal suddenness (64) The commonest symptom of hemorrhagic disease of the newborn is bleeding into the gastrointestinal tract resulting either in hematemesis or melena (64 115) In other cases oral, nasal cutaneous or even intracranial bleeding may occur Hemorrhage from the umbilical stump or site of circumcision is also common Massive hemorrhage is unusual More often bleeding is slow but persistent (715) and may be of such proportions that the infant goes into shock If untreated as many as a third of the infants may die (106 64 115) In fatal cases hemorrhages are often found in the parenchyma of the adrenals kidneys liver and other organs

The pathogenesis of deficiencies of prothrombin the stable

serum factors and Christmas factor in the newborn infant has been studied intensively These factors require Vitamin K for their formation At first the newborn infant must depend upon the residue of the Vitamin K which crossed the placenta before birth and the small amounts present in milk (519) Dam and his associates (138) pointed out that the concentration of prothrombin falls more rapidly in breast fed than in artificially fed infants cow's milk contains four times as much Vitamin K as human milk. As bacteria grow in the intestinal tract of the newborn infant the supply of Vitamin K rapidly increases The importance of these organisms is evidenced by the appearance of hemorrhagic disease in infants treated with antibiotics during the first days of life

Why hemorrhagic disease occurs in some newborn infants and not others is not clear It is more frequent during the Winter and Spring than in the Summer and Autumn but no explanation for this seasonal change is forthcoming (686) The infants who are most susceptible to the disease include those born prematurely those who have had evidences of asphyxia *in utero* those who have had a traumatic birth and those with infantile diarrhea

The diagnosis of hemorrhagic disease of the newborn is based upon the characteristic clinical picture associated with a long prothrombin time and a long clotting time One must distinguish its symptoms from other bleeding phenomena in the newborn infant The retinal hemorrhages which are found in about a third of all newborn infants are probably not evidences of hemorrhagic diseases of the newborn Cutaneous petechiae of no ultimate significance are often seen within a few hours after birth and are apparently due to the mechanical stresses of parturition Another common lesion is subperiosteal hemorrhage over the parietal bones caused by periosteal injury during delivery Such cephalohematomas usually resolve without treatment Intracranial bleeding nearly always the result of birth injury is more serious and may lead to death or permanent injury Except in the premature infant intracranial bleeding is usually associated with a difficult delivery

A relatively good technique for the prophylaxis of hemorrhagic disease of the newborn was introduced by several groups about 1939 (141 686 594 278) Vitamin K given either to the mother

during the last day or two of pregnancy or to the newborn infant ameliorates the coagulative abnormalities and decreases the incidence of hemorrhagic disease For example 10 mg of 2 methyl 1-4 naphthoquinone administered parenterally to the mother within a few hours before delivery significantly decrease the incidence of bleeding and death from hemorrhagic disease in the newborn Or one mg of Vitamin K_1 may be given every twenty four hours to the newborn infant for about five days Although prophylaxis is not complete, there are serious dangers associated with increasing the dosage of Vitamin K Allison (35) seeking to decrease the incidence of hemorrhagic disease still further found that excessive amounts of Vitamin K cause hyperbilirubinemia This hyperbilirubinemia is due to excessive hemolysis associated with the appearance of inclusion bodies in the erythrocytes As little as 10 mg of Synkavite per day for the first three days of life has been enough to produce fatal kernicterus The mechanisms leading to hemolysis are under intensive study (724 444) Excessive amounts of Vitamin K may also cause the infant to go into shock or to have convulsions For these reasons only small amounts of Vitamin K are recommended for the prophylaxis of hemorrhagic disease even though larger doses might give more complete protection

The treatment of hemorrhagic disease of the newborn consists principally in the transfusion of small amounts of blood (106) The blood need not be fresh for stored blood contains adequate amount of the Vitamin K dependent clotting factors If bleeding is not dramatic one may afford to delay transfusion and give 1 or 2 mg of Vitamin K_1 intramuscularly or intravenously instead If the infant is bleeding from the gastrointestinal tract many believe that there is no need to withhold food Using the regimen outlined the prognosis should be excellent

HEREDITARY DEFICIENCIES OF THE VITAMIN K DEPENDENT CLOTTING FACTORS

Hereditary Deficiency of Prothrombin An isolated deficiency of prothrombin itself is most exceptional In nearly every reported case some other abnormality has ultimately been demonstrated However, the patients described by van Creveld (673) Quick

(522) and Borchgrevink (83) probably do have congenital deficiencies of prothrombin These patients have had moderately severe life long bleeding tendencies characterized by bleeding after surgical procedures dental extractions and injuries hematuria bleeding into muscles and joints and menorrhagia Fortunately permanent joint deformities have not been observed The deficiency has appeared in both sexes and is familial The sparce data available can be interpreted to mean that a deficiency of prothrombin results from the inheritance of non sex linked recessive genes (83)

In the reported cases the one stage prothrombin time has been moderately prolonged though not to the degree observed with deficiencies of pro-SPCA or Stuart factor This is partly due to the fact that the one-stage prothrombin time is more sensitive to deficiencies of these two serum factors than to prothrombin itself To establish the diagnosis the deficiency of prothrombin should be demonstrated by tests specific for this substance the defect should not be corrected by the addition of barium sulfate adsorbed plasma (which contains proaccelerin) or serum (which contains pro SPCA and Stuart factor) Moreover care must be taken to exclude the presence of a circulating anticoagulant In the reported cases the deficiency of prothrombin has not been absolute the concentration of prothrombin has been estimated to be about 10 per cent of normal (83)

Little is known about the therapy of this rare condition In only one case has the administration of Vitamin K had even a partial corrective effect (522) Reports of the effect of blood transfusion have been conflicting One patient did not respond to this procedure (673) while in another the concentration of prothrombin rose to the predicted degree after transfusion (83)

Minor discrepancies in laboratory data among these few cases raise the question of whether they are all examples of the same disorder Additional cases of prothrombin deficiency have been described in association with other defects in the clotting mechanism but caution should be used before ascribing such combined abnormalities to a hereditary defect

Hereditary Deficiencies of the Stable Serum Factors Pro-SPCA and Stuart Factor In the 1940 s a number of patients were

reported to have hereditary prothrombin deficiencies In some of these cases the defect was corrected by the addition of serum, which is poor in prothrombin This confusion was clarified by Alexander (28) in a study of a young girl whose one stage prothrombin time was greatly prolonged The abnormality measured in this test was corrected by the addition of serum Since serum is devoid of prothrombin and proaccelerin, Alexander assumed that the patient s plasma lacked some additional substance Just such a substance had been described by many workers in the preceding few years under such names as co thromboplastin, stable factor, proconvertin and the precursor of either factor VII or serum prothrombic conversion accelerator (pro-SPCA) Alexander showed that the addition of preparations rich in pro SPCA corrected the defect measured in this patient s plasma

Since then many cases have been described in which a bleeding tendency has been associated with the presence of an abnormally long one stage prothrombin time, correctible by the addition of serum These cases do not form a homogeneous group, and despite considerable recent progress, cannot be classified rationally (534) They seem to fall into two general groups, those which seem to coincide with Dr Alexander s case of pro SPCA deficiency and those which seem to have a defect described by Telfer (656) and by Hougie and Graham (292 245) as deficiency of Prower or Stuart factor

The symptoms exhibited by patients in each of the two disorders are not yet distinguishable Both sexes are involved with equal frequency Bleeding usually begins in earliest infancy The hemorrhagic symptoms are similar to those of hemophilia but are usually relatively mild Bleeding from the umbilicus is common just after birth In affected females, menorrhagia is frequent and severe hemorrhage may occur during childbirth (172) In these cases, the first few menstrual periods at the menarche are likely to be especially severe These young girls may require hospitalization and repeated transfusions If possible hysterectomy should be avoided since the menorrhagia tends to subside after several cycles Unfortunately, this operation has been performed in several reported cases Surgical procedures may be tolerated surprisingly well Death attributable to bleeding is uncommon

The differentiation of the two groups of cases is based upon laboratory studies In both the one stage prothrombin time is long In patients deficient in pro SPCA the clotting time in glass tubes may either be normal or long the bleeding time is occasionally prolonged The prothrombic activity of serum that is the amount of prothrombin remaining after blood has clotted is usually normal A popular explanation of these observations is that pro SPCA is needed for the action of tissue thromboplastin but not for the action of thromboplastin evolving from the blood itself Indeed in some cases the thromboplastin generation test has been normal supporting this view However this explanation is not entirely satisfactory The clotting time is often prolonged and in many cases including one studied at University Hospitals of Cleveland the thromboplastin generation test is abnormal Thus the site of action of pro-SPCA remains to be determined Its physiologic role is similarly poorly delineated It seems to be present in plasma as a precursor which is activated during clotting but how the active form then promotes the formation of thrombin is obscure (23) The diagnosis of pro SPCA deficiency rests upon two criteria The clotting time of plasma in the presence of Russell s viper venom is normal this venom substitutes in an unexplained way for the biological activity of pro-SPCA (311) And the plasma of the patient known to have pro SPCA deficiency does not correct the patient s defect

The deficiency of pro SPCA is usually not absolute Hemorrhagic symptoms appear when the concentration of this factor is about 10 per cent of normal or less (23) Chevallier (111) noted that the plasma of one of his patients inactivated the pro SPCA of normal plasma Anticoagulants have not been described in other cases nor have any been detected in the four patients studied at University Hospitals of Cleveland

In the second group of cases deficient in Prower or Stuart factor tests of clotting time serum prothrombic activity and thromboplastin generation give abnormal results and Russell s viper venom fails to correct the defect The diagnosis is established by the failure of the plasma to correct or be corrected by plasma from patients known to have Stuart factor deficiency A satisfactory assay for Stuart factor has been published which is

useful when plasma from such patients is not available (604) Unfortunately, the differentiation between pro SPCA and Stuart factor deficiencies is not as clear cut as this brief summary suggests, and only further studies will clarify the problem

The mode of inheritance of deficiencies of these stable serum factors is only partly understood Both familial and sporadic cases of each have been observed In one family studied at University Hospitals of Cleveland two siblings have pro SPCA deficiency, as measured in the laboratory, although only one has clinical symptoms (534) Both parents have a partial deficiency of pro SPCA In another fatal case, both parents are normal but since this child survived for only a few months the possibility was not excluded that the disease was not hereditary These data are compatible with the view that pro SPCA is the result of the inheritance of partially recessive abnormal genes Evidence supporting this view has been published by Owren (476) Long (374) and Dische and Benfield (172) The same pattern of inheritance is apparently operative in Stuart factor deficiency The heterozygous carriers are either asymptomatic or have mild symptoms and their plasma is slightly deficient in Stuart factor (245) In one interesting case a heterozygous carrier also had alcaptonuria (562) a defect noteworthy because of the vague structural similarity between homogentisic acid whose metabolism is impaired in alcaptonuria and the naphthoquinone portion of the Vitamin K molecule

Although stable factor deficiencies are seldom lethal death may occur either from exsanguination or from bleeding into the central nervous system Treatment is unsatisfactory The transfusion of blood or plasma seems to be only of the most transient benefit The corrective effect of transfusion is dissipated within less than 24 hours (28) Occasionally it is said that the administration of large amounts of Vitamin K will produce a partial transient response in patients with pro SPCA deficiency, but by and large this method of therapy is unsatisfactory

At present the differentiation between pro SPCA and Stuart factor deficiency is only of theoretic interest Further studies are needed before the distinction acquires practical utility

Other Hereditary Deficiencies of Vitamin K Dependent Clot

ting Factors Hereditary deficiencies of Christmas factor are described in Chapter IV, and hereditary combined deficiencies of the Vitamin K-dependent clotting factors in Chapter X.

SELECTED REFERENCES

1 Aballi, A J., Lopez Banus V de Lamerens S and Rozengvaig S Coagulation studies in the newborn period Alterations of thromboplastin generation and effects of Vitamin K in full term and premature infants *A.M.A J Dis Child* 94 589 1957

23 Alexander B Clotting factor VII (proconvertin) Synonymy properties clinical and clinicolaboratory aspects *New Eng J Med* 260 1218 1959

138 Dam, H Dyggve H., Larsen H and Plum, P The relation of Vitamin K deficiency to hemorrhagic disease of the newborn, *Adv Ped* 5 129 1952

333 Koller F (moderator) Side-effects and contraindications of anticoagulants *Thrombosis et Diathesis Haemorrhagica* 2 604 1958

522. Quick, A J Pisciotta A V and Hussey C V Congenital hypoprothrombinemic states *A.M.A Arch Int Med* 95 2 1955

Chapter VIII

PARAHEMOPHILIA

PARAHEMOPHILIA is a life-long hemorrhagic disease of both sexes in which the concentration of proaccelerin in plasma is greatly reduced Since proaccelerin is needed for the conversion of prothrombin to thrombin the one stage prothrombin time is prolonged About twenty five affected families have been found since Owren (475) described the disease The severity of bleeding varies from case to case In mild instances there may be spontaneous epistaxes easy bruisability menorrhagia and excessive bleeding after dental extractions or surgical procedures In other cases bleeding may be severe or even fatal The patient may have hematomas gingival bleeding bleeding into the central nervous system, intra ocular hemorrhage hematemesis or other types of bleeding Hemarthrosis has not been described As in the case of hemophilia there is some evidence that bleeding may occur in crops For example my patient vomited blood a few days after extensive hematomas appeared on his extremities (585)

Parahemophilia is usually but not invaribly familial (92) The patient s parents may have partial deficiencies of proaccelerin with or without mild symptoms In my own patient the concentration of proaccelerin in his mother s plasma was about 50 per cent of normal his father was not available for study (585) In other cases both parents may be normal (476) Sometimes the patients have resulted from consanguineous unions These observations fit the hypothesis that the genes responsible for the appearance of parahemophilia are recessive (330) However in other cases the abnormal genes seem to behave in a dominant fashion This may indicate that a deficiency of proaccelerin may be caused by each of several genetic defects Cases have been described in association with congenital cardiovascular disease

syndactylism and epidermolysis bullosa congenitalis A concomitant deficiency of antihemophilic factor has also been noted in a few patients (see page 104)

The site of synthesis of proaccelerin is unknown The depressed concentration of this protein in the plasma of patients or animals with hepatic damage suggests that the liver is needed in its synthesis (649) The administration of aminophylline is said to increase the concentration of proaccelerin in canine plasma (382) but it is ineffective in human cases of parahemophilia (92)

Proaccelerin behaves like a relatively labile plasma protein At refrigerator temperatures it disappears rapidly from oxalated plasma but more slowly from citrated plasma (197) Proaccelerin is destroyed by gentle heating trypsin or plasmin but resists treatment with sulfhydryl containing reagents (536) It can be absorbed from plasma by barium stearate but not by barium sulfate (684) Activity attributable to proaccelerin is destroyed or consumed during clotting so that serum is ordinarily devoid of proaccelerin bovine serum is an exception

The action of proaccelerin is unknown In parahemophilia the patient s plasma clots normally upon the addition of thrombin but the one stage prothrombin time is long For this reason it is assumed that proaccelerin acts in the middle stages of the clotting process the conversion of prothrombin to thrombin Appropriate studies suggest that it acts after the interaction of the antihemophilic factor Christmas factor Hageman factor and platelets (177) Its relationship to the action of the stable serum factors is not clear

During clotting proaccelerin acts as if it is changed to an active form accelerin (475) Experimentally the conversion of proaccelerin to accelerin can be initiated by preparations of thrombin (694) This observation has suggested that clotting may be a chain reaction so that the thrombin which evolves induces the formation of accelerin and this in turn speeds the evolution of more thrombin Proaccelerin may be changed to accelerin in the absence of thrombin by Russell s viper venom (287)

Whether the platelets of a parahemophiliac contribute to his bleeding tendency is unclear Alexander and Goldstein (26)

showed that the agglutination of platelets may be retarded in parahemophilic blood Normal platelets have proaccelerin like activity (693), whereas those obtained from patients with para hemophilia lack this property This proaccelerin like activity of normal platelets is probably due to the adsorption of proaccelerin from plasma for one can induce normal proaccelerin like activity in parahemophilic platelets by incubating them in normal plasma (288)

The diagnosis of parahemophilia is readily made The abnormally long one stage prothrombin time is corrected by the addition of fresh oxalated plasma, which has been adsorbed with barium sulfate to remove prothrombin and the stable serum factors This test alone will not exclude a deficiency of fibrinogen for which appropriate tests must be performed The failure of serum or aged or heated plasma to correct the defect confirms the diagnosis In severe parahemophilia little or no proaccelerin is detectable in the plasma but bleeding symptoms are said to occur in patients in whom the concentration of this factor is reduced only to 30 per cent of normal (199) Other tests of hemostatic function mav be abnormal The clotting time and partial thromboplastin time may be prolonged and the serum prothrombic activity is usually abnormally high The results of the thromboplastin generation test are abnormal but the defect is clearly demonstrable only if the incubation mixture contains the patient s own platelets or crude cephalin since the proaccelerin like activity of normal platelets may obscure the abnormality Circulating anticoagulants which inactivate proaccelerin have been described (290 204) The bleeding time is ordinarily normal

The prognosis of parahemophilia is reasonably good with regard to life although deaths have been reported One patient exsanguinated with her first menstrual period Hematomas may cause transient disability but crippling arthritis is unknown Treatment consists of local hemostatic measures and if needed the transfusion of citrated blood or plasma Although proaccelerin is labile enough remains in citrated bank blood to be therapeutically useful within the usual period of storage An initial dosage of 10 cc of fresh citrated plasma per kilogram of body weight has been suggested (199) However the transfusion of blood or

plasma must be repeated at frequent intervals for half of the proaccelerin in transfused blood disappears within about twenty hours Vitamin K has no place in the treatment of parahemophilia since it is unconcerned with the synthesis of proaccelerin

A deficiency of proaccelerin may also occur as an acquired abnormality Significant deficits of this protein have usually been associated with hepatic disease (269, 265 209), but are also observed in association with sepsis scarlet fever, polycythemia vera carcinoma of the prostate and tuberculosis (199) A deficiency of proaccelerin may also complicate acquired hypofibrinogenemia such as may occur in obstetrical hemorrhagic accidents In this situation the proaccelerin may be consumed during intravascular coagulation or destroyed by the proteolytic activity of plasmin Except for their later onset the symptoms in these acquired cases do not differ from those of congenital parahemophilia However in the majority of the acquired cases the effects of other concomitant defects may dominate the clinical picture

SELECTED REFERENCES

26 Alexander B and Goldstein, R Parahemophilia in three siblings (Owren s disease) with studies on certain plasma components affecting prothrombin conversion *Am J Med* 13 255 1952

199 Fantl P *Parahemophilia (Proaccelerin Deficiency) Occurrence and Biochemistry in Hemophilia and Hemophilioid Diseases* K. Brinkhous edit Chapel Hill U of N Carolina Press 1957

475 Owren P A Coagulation of blood Investigation of new clotting factor *Acta Med Scand Suppl 194* 1 1947

Chapter IX

HYPOFIBRINOGENEMIC AND AFIBRINOGENEMIC STATES

FIBRINOGEN is the precursor of fibrin the protein of which the clot is composed Under many circumstances hemostasis fails because insufficient fibrinogen is available for the formation of an adequate clot, or because the fibrin clot is unstable and dissolves Normally the concentration of fibrinogen averages about 270 mg per 100 ml of plasma in males and 300 mg per 100 ml in non pregnant females (544) The variation among normal individuals is wide but in any one person the concentration of fibrinogen during health is relatively constant In adults the circulating plasma contains at least 10 grams of fibrinogen It has been estimated that only about half of the body s available fibrinogen is in the circulating plasma at any one time so that in adults the total pool of this protein is about 20 grams Since the half life of fibrinogen is normally about three to four days (680) about 3 grams must be synthesized each day to replace the amount which has been catabolized

The formation of fibrinogen requires the presence of functional hepatic tissue This need was demonstrated indirectly by Doyon (183), Whipple (708) Jones and Smith (315) and others who found that the concentration of fibrinogen fell after hepatectomy or the administration of hepatotoxins Rarely too patients with severe hepatic disease have hypofibrinogenemia (209) More direct evidence of the role of the liver was obtained by Miller (436 435) who showed that the isolated liver synthesizes fibrinogen while an animal from which the liver has been removed cannot perform this function

The forces which influence the rate of synthesis of fibrinogen

are unknown The administration of ACTH and cortisone may decrease (202) and of pituitary growth hormone may increase (105) its concentration in plasma Its concentration is also influenced by diet the ingestion of cooked pig stomach increases the concentration of fibrinogen in canine (215) or human (256) plasma During pregnancy in various inflammatory conditions and after injury or surgical procedures the concentration of fibrinogen may be elevated a change which contributes to the rapid sedimentation rate frequently found in these conditions (256) Less commonly the concentration of fibrinogen may be depressed below normal a state referred to as hypofibrinogenemia or fibrinogenopenia Rarely no fibrinogen at all is detectable in peripheral blood that is there is afibrinogenemia a term often incorrectly applied to hypofibrinogenemic states

The metabolic fate of fibrinogen is unknown Some may be consumed in the healing of everyday minor injuries Years ago Whipple pointed out that clotting must take place continually in normal individuals to heal those trivial wounds from which patients with bleeding tendencies seem to bleed spontaneously" Considerably larger amounts of fibrinogen may be lost from the body during a major hemorrhage for each liter of blood lost contains about 1 5 grams of this protein If utilization or loss is rapid and extensive the rate of synthesis may be exceeded so that the concentration of circulating fibrinogen decreases

Fibrinogen may also be consumed by intravascular clotting if thromboplastic material inadvertently enters the blood stream Woolridge in 1886 reported that the slow intravenous injection of tissue thromboplastin makes the blood of an experimental animal incoagulable About thirty five years later Mills (437) found that the injection of thromboplastin decreases the concentration of fibrinogen in the circulating blood presumably because the protein is consumed in intravascular clotting That such intravascular clotting may take place had been demonstrated by Obato (467) who found thrombi in the smaller blood vessels after the injection of thromboplastin The rapid injection of tissue thromboplastin may be lethal Large clots may form in the lumens of the pulmonary artery inferior vena cava or the portal vein obstructing the circulation When the thromboplastin is injected more slowly

defibrination may occur without obvious disability although the animal bleeds if subjected to minor injury (539, 272) Several hours after an infusion of tissue thromboplastin is completed the concentration of fibrinogen begins to rise within twenty four hours the level is higher than in an untreated animal Other alterations may accompany the intravenous injection of thromboplastin The clotting time lengthens the platelet count falls and the thrombin time may increase In some cases the fibrinolytic activity of the plasma is exaggerated A decrease in the concentration of antihemophilic factor has also been described (482)

The changes which follow the intravenous injection of clot promoting agents are strikingly similar to those observed in some patients with acute hemorrhagic disorders particularly in association with childbirth This similarity has suggested that in some cases clinical hypofibrinogenemia may be due to the consumption of fibrinogen in intravascular clotting Whether the same process of intravascular defibrination normally goes on in miniature all the time is not known

Another pathway through which fibrinogen may be consumed is in the extravascular deposition of fibrin in inflammatory exudates Again whether this process normally takes place continually to a minor degree contributing to the catabolism of fibrinogen is unknown

Considerable attention has been paid to the possibility that fibrinogen may be metabolized through the digestive action of plasmin, a proteolytic enzyme of plasma Normally this enzyme is principally in the form of an inactive precursor plasminogen *In vitro*, plasminogen can be activated by the addition of certain organic solvents such as chloroform by streptokinase, a principle found in cultures of beta hemolytic streptococci by tissue particles or by urokinase a substance extracted from urine The mechanism by which these substances activate plasminogen is under sharp debate (38, 592) Plasma also provides inhibitors directed against plasmin which may protect against the inappropriate action of this enzyme

Active plasmin hydrolyzes fibrinogen and fibrin at comparable speeds Still when streptokinase is added to plasma fibrinogen is digested slowly When the mixture is allowed to clot the fibrin which forms is digested rapidly This seeming inconsistency

acceleration of the action of plasmin in the presence of a clot is also noted when the enzyme is activated "spontaneously" or by chloroform The fibrin clot seems to speed the activation of plasminogen perhaps because the enzyme is adsorbed by the fibrin and in this way is separated from its inhibitors in plasma While at first blush these considerations seem abstruse they are of great practical importance for they help to explain the presence of fibrinogen in blood which once clotted is highly fibrinolytic Moreover these observations rationalize the fact that experimentally produced thrombi may be lysed by the intravenous injection of streptokinase without unduly depressing the concentration of fibrinogen in the plasma

Fibrinogen and fibrin are by no means the only natural substrates of plasmin for proaccelerin antihemophilic factor and to a lesser extent Christmas factor and prothrombin may also be digested by this enzyme (176) Moreover plasmin inactivates ACTH glucagon somatotropin (440a) and complement the last action mediated through the first of the four recognized components of this complex (495) These complicated effects must be kept in mind as therapeutic preparations of plasmin or streptokinase become available for the treatment of intravascular thromboses They also accent the diverse changes to be expected with intravascular fibrinolysis

The physiologic role of plasmin is uncertain One wonders if this enzyme helps to dissolve the intravascular thrombi which may form in the smallest blood vessels in response to everyday injuries However its physiologic function may be quite different since nothing is known concerning the significance of its action upon immune complement

HYPOFIBRINOGENEMIC STATES

Hypofibrinogenemia may result from a decrease in the rate of synthesis of fibrinogen from extravascular sequestration of this protein from consumption in intravascular coagulation from the destruction of fibrinogen or fibrin by plasmin from an alteration in the fibrinogen molecule such that it can neither function normally nor be detected by ordinary chemical means and under certain circumstances from loss of blood by hemorrhage

When the concentration of fibrinogen in the circulating plasma

falls to about 100 mg per ml of plasma or less bleeding may occur The patient may experience epistaxes cutaneous ecchymoses after trivial injury, gingival bleeding hematuria, melena bleeding into the central nervous system, or bleeding at the sites of venipuncture or parenteral injections The tendency to severe hemorrhage after injury, surgical procedures or childbirth is of especial importance Nonetheless if they are not exposed to injury patients with hypofibrinogenemia or afibrinogenemia may be free of bleeding symptoms for long periods—even months or years

Hypofibrinogenemia or afibrinogenemia can be detected qualitatively by inspecting the clot formed upon adding thrombin to the patient s blood or quantitatively by chemical analysis (427) A useful technique for the measurement of fibrinogen in an emergency was suggested by Page (408 545) The operating room is provided with scrupulously clean Pyrex glass test tubes 13 by 100 mm in size scored at the 1 cc mark and containing 0 1 cc of topical thrombin solution (1 000 National Institutes of Health units per cubic centimeter) This is the same topical thrombin preparation found in most surgeries and emergency wards These thrombin tubes are stored in a freezer When hypofibrinogenemia is suspected a sample of venous blood is obtained and the thrombin tube filled to the 1 cc mark If the blood does not clot when mixed with thrombin it probably contains no fibrinogen If fibrinogen is present in abnormally low concentrations a clot forms which may at first appear to be normal in appearance However, after a few minutes it shrivels to a small size either spontaneously or upon gentle tapping of the tube A firm clot of good size suggests that a normal amount of fibrinogen is present in the blood Obviously, it is important to have personal experience with the appearance of normal thrombin clots prior to the use of the test in an emergency This test has proved to be a reliable index of the presence of hypofibrinogenemia or afibrinogenemia in cases of acute obstetric hemorrhage

Despite reports to the contrary the clotting time is an unreliable measure of hypofibrinogenemia for the results of this test may be normal even though the concentration of fibrinogen is critically low Other tests of the clotting mechanism are normal unless the concentration of fibrinogen influences the determina

tion Thus in hypofibrinogenemia the results of the thromboplastin generation test and serum prothrombic activity are normal but unless fibrinogen is added to the reaction mixture the thrombin and prothrombin times may be abnormally long In many circumstances hypofibrinogenemia or afibrinogenemia may be accompanied by other coagulative defects these will be described in subsequent portions of this chapter In patients with severe hypofibrinogenemia or afibrinogenemia the bleeding time may be normal or prolonged However the incision tends to break open after bleeding has apparently stopped and blood may continue to ooze from the wound for hours

The treatment of hypofibrinogenemia or afibrinogenemia depends to some degree upon the pathogenesis of the abnormality In general replacement therapy is used only to treat hemorrhage or as a prophylactic measure during parturition or surgery The treatment of choice is the intravenous injection of human fibrinogen usually prepared by a modification of the method of Cohn Fibrinogen for intravenous use is available through the American Red Cross or commercially from the Cutter Laboratories Berkeley California Under most circumstances the initial dosage is 4 to 6 grams Whole blood or plasma is not effective because of the huge volume needed to provide the required amount of fibrinogen Since fibrinogen for intravenous injection is prepared from pooled plasma its use entails a high risk of inducing homologous serum jaundice (606) a complication detected in as many as 20 per cent or more of treated patients In addition to the risk of hepatitis the possibility that widespread intravascular deposition of fibrin may follow the administration of fibrinogen must be considered (249)

CONGENITAL AFIBRINOGENEMIA

Surprisingly an occasional individual is born in whom the plasma contains no significant amount of fibrinogen as measured by chemical immunological or electrophoretic means Needless to say the blood of such patients is incoagulable and does not clot upon the addition of thrombin Moreover the tissues themselves do not contain fibrinogen

Patients with congenital afibrinogenemia may bleed from the

umbilicus at birth (675) Throughout their lives, they may have repeated episodes of severe bleeding—ecchymoses epistaxes hematomas, hemoptyses bleeding into the gastrointestinal tract or central nervous system and so forth In one individual hemorrhage occurred after rupture of the spleen Hemarthroses are relatively rare Permanent damage to tissues is uncommon perhaps because of the absence of fibrin (71) Minor injuries or surgical procedures are followed by protracted bleeding Death results from blood loss or from bleeding into a vital area Surprisingly the patients may have long periods of freedom from bleeding (675) Moreover girls with this disorder who have reached their menarche have nearly normal menses (354) The very fact that these individuals survive to adult life suggests the importance of vascular factors in hemostasis

Platelet function appears to be normal in patients with congenital afibrinogenemia In studies of Pinniger and Prunty (496) and others the platelets have behaved normally in many tests *in vitro* Alexander and his associates (29) believe that platelet agglutination and lysis in these patients is due to the elaboration of thrombin which is unimpaired in afibrinogenemia Thus clotting mechanisms may play a role in hemostasis even though a fibrin clot does not form

Congenital afibrinogenemia is an inherited disease of both sexes but for some unexplained reason many more cases have been reported in males than in females (243) Several cases may occur within a family always in the same generation In addition a number of cases have resulted from consanguineous marriages These observations suggest that the abnormal gene responsible for the defect is recessive or to put it another way one need inherit only one normal gene to synthesize adequate amounts of fibrinogen The heterozygous state in which the individual has one normal and one abnormal allele of a gene required for the synthesis of fibrinogen is usually not detectable (243) However, some heterozygous carriers are said to have moderate hypofibrinogenemia and isolated cases of hypofibrinogenemia have been described (554) Possibly in different families the heterozygous state is manifest in different ways

All the available evidence suggests that in congenital afibrino

genemia the patient cannot synthesize fibrinogen After the transfusion of citrated blood or purified preparations of fibrinogen this protein may be detected in the blood stream for as long as seventeen days although concentrations effective for hemostasis are maintained for a much shorter time Gitlin and Borges (233) showed that the half life of infused fibrinogen is four days a figure comparable to the half life of fibrinogen in normal individuals (680) Thus the destruction or utilization of fibrinogen is not excessively rapid The defect in synthesis appears to be limited to this single substance

The diagnosis of congenital afibrinogenemia is readily made since peripheral blood is incoagulable even when thrombin is added As one would expect the one stage prothrombin time is infinite The absence of fibrinogen should be confirmed chemically or immunologically and the presence of an anticoagulant active at the last stage of coagulation should be excluded Assays for other clotting factors usually give normal results although mild and transient thrombocytopenia and slight depression of the concentration of proaccelerin have been reported The bleeding time may be normal or prolonged However when the bleeding time is normal bleeding may start afresh if the finger is flexed shortly after the completion of the test The tourniquet test is normal

Treatment is indicated only during episodes of bleeding or to prevent hemorrhage during surgical procedures The transfusion of concentrated fibrinogen is much more effective than whole blood or plasma Four grams of fibrinogen given intravenously to an adult usually raises the concentration of fibrinogen to levels providing hemostasis Repeated injections may be needed before bleeding is controlled In addition to the risk of homologous serum jaundice treatment may be complicated by the appearance of anticoagulant substances which seem to be directed against fibrinogen (97)

The prognosis of this disorder is relatively poor many patients die either in infancy or in childhood (675) However with care patients with congenital afibrinogenemia can reach adult life It is too soon to say whether they can be nursed along through a reasonable life span

FIBRINOLYTIC PURPURA

The existence in plasma of enzyme systems which can digest fibrin has led to frequent speculation about their role in the pathogenesis of bleeding In innumerable cases hypofibrinogenemia or afibrinogenemia has been attributed to the action of plasmin, a proteolytic enzyme of plasma (see page 82) However in only a few of these cases is the evidence which links fibrinolysis to bleeding convincing Several technical difficulties may lead to an incorrect diagnosis of fibrinolytic purpura When hypofibrinogenemic blood coagulates the clot at first may seem to be normal in size The clot then retracts rapidly to form a tiny ball of fibrin easily lost among the red cells extruded from the clot This makes it appear as if the clot has lysed Another difficulty is more subtle The time which elapses until a clot dissolves is proportional to the initial size of the clot formed As a result the clot formed from a blood whose fibrinogen content is abnormally low may lyse more rapidly than normally Under these conditions rapid lysis of clotted blood or plasma is probably without significance (14)

Either whole blood or plasma may be used to measure the rate of fibrinolysis Normal plasma clotted by the addition of thrombin or calcium does not lyse for at least forty eight hours when incubated at 37° under sterile conditions After exercise anxiety, electroconvulsions childbirth or the injection of adrenalin lysis may be more rapid so that the clots formed *in vitro* dissolve within a day or less (390 200, 538) Under these circumstances lysis is seldom complete until several hours have passed Rapid clot lysis as measured in the test tube is also observed in the blood of patients with hemorrhagic shock (652) The significance of the fibrinolysis initiated by these stresses is not clear It seems improbable that bleeding could result from the degree of fibrinolytic activity observed More reasonably the significance of lysis in these conditions is limited to the possibility that clots are removed too rapidly from the sites of injury

Increased fibrinolytic activity is also an almost constant concomitant of cirrhosis of the liver and less frequently of acute hepatic disease (240 529) However it is difficult to demonstrate a correlation between increased fibrinolysis and the hemorrhagic

tendency of patients with hepatic disease Indeed the severest bleeding is found in patients with acute yellow atrophy, a syndrome in which accelerated fibrinolysis is uncommon More likely bleeding in patients with hepatic disease is related to deficiencies of the Vitamin K-dependent clotting factors proaccelerin and platelets Rarely patients with hepatic disease may have hypofibrinogenemia or even afibrinogenemia but in these cases evidences of rapid fibrinolysis are unusual (48) More commonly the concentration of fibrinogen in the plasma of patients with hepatic disease is either normal or slightly elevated (256)

Very rarely a bleeding tendency does seem to be related to excessive fibrinolysis *in vivo* In these cases of *fibrinolytic purpura* fibrinogen may be present in the peripheral blood although often its concentration is somewhat decreased Nonetheless the blood is either incoagulable or its clotting is delayed If a clot does form it redissolves within a few minutes Under these conditions fibrinolytic activity is best demonstrated in plasma clotted by thrombin The clot may completely dissolve within a few minutes These criteria are fulfilled in only a few of the reported cases Tagnon (652) for example described rapid clot lysis in association with severe postpartum hemorrhage Fibrinolytic purpura has also been observed in patients undergoing a variety of surgical procedures such as pulmonary operations (620) prostatectomy (373) splenectomy (579) and excision of a cavernomatous hemangioma (232) A case we reported may have been related to surgery but the pathogenesis of the fibrinolysis was uncertain

A 42 year old woman with adenocarcinoma of the pancreas oozed almost continually from the serosal surfaces during an exploratory laparotomy A second operation three weeks later was interrupted after 45 minutes by hypotension and oozing of blood from serosal surfaces The hemorrhage became uncontrollable but no single bleeding point could be found Despite the transfusion of 4 liters of blood the patient expired 5 hours after the operation had begun At the time of death 5 liters of unclotted blood had collected in the peritoneal cavity and the patient had hematomas at the sites of venipunctures and evidences of gastrointestinal bleeding Two hours after bleeding began her venous blood was incoagulable Plasma prepared from this blood did clot but lysed completely 11 minutes later

FIBRINOLYTIC PURPURA

The existence in plasma of enzyme systems which can digest fibrin has led to frequent speculation about their role in the pathogenesis of bleeding In innumerable cases, hypofibrinogenemia or afibrinogenemia has been attributed to the action of plasmin, a proteolytic enzyme of plasma (see page 82) However, in only a few of these cases is the evidence which links fibrinolysis to bleeding convincing Several technical difficulties may lead to an incorrect diagnosis of fibrinolytic purpura When hypofibrinogenemic blood coagulates the clot at first may seem to be normal in size The clot then retracts rapidly to form a tiny ball of fibrin easily lost among the red cells extruded from the clot This makes it appear as if the clot has lysed Another difficulty is more subtle The time which elapses until a clot dissolves is proportional to the initial size of the clot formed As a result, the clot formed from a blood whose fibrinogen content is abnormally low may lyse more rapidly than normally Under these conditions rapid lysis of clotted blood or plasma is probably without significance (14)

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tract immediately *post partum*—or to cervical or vaginal lacerations However when uterine bleeding is fatal abnormalities in the blood clotting mechanisms are usually present (545) The commonest change detected is a decrease in the concentration of fibrinogen in the circulating plasma but other hemostatic defects may contribute to the bleeding tendency

During normal pregnancy the concentration of fibrinogen gradually rises from an average of about 300 mg per 100 cc of plasma in non pregnant women to about 450 mg per 100 cc in the 37th week of pregnancy and thereafter The magnitude of the rise varies widely from individual to individual (538) The concentrations of prothrombin (33) pro-SPCA (157 33) Christmas factor (541) and probably Stuart factor also increase impressively On the other hand the concentrations of proaccelerin antihemophilic factor Hageman factor and platelets remain at their pre pregnancy levels (541) and there is no evidence of increased plasma fibrinolytic activity (538 415)

During normal labor and immediately after delivery few changes occur in the clotting mechanism that can be measured in the test tube The clotting time and the one stage prothrombin time are unaltered and the slight variation which occurs in the concentration of fibrinogen and platelets is inconstant During the hours after delivery a moderate increase in fibrinolytic activity is common (538 415) clotted plasma dissolving within less than a day The pathogenesis of the increased rate of fibrinolysis is unknown but changes of this magnitude are observed in normal non pregnant individuals subjected to mild physical or emotional stress and are probably not sufficient to induce a bleeding tendency

The control of uterine bleeding after delivery depends upon several factors Immediately after delivery myometrial contraction constricts the uterine blood vessels checking the flow of blood from the placental site The role of clotting in the control of bleeding immediately *post partum* is unclear Greenberg (252) showed that the blood expelled from the uterus after the separation of the placenta is usually incoagulable Furthermore Barnes (42) pointed out that this blood is defibrinated and clots only upon the [illegible] clots do not dissolve abnor

The patient's plasma contained at least 105 mg of fibrinogen per 100 ml the platelet count was 68 000 and the one stage prothrombin time somewhat prolonged possibly a reflection of the low fibrinogen The titer of antihemophilic factor was normal no anticoagulant was demonstrable The conclusion was reached that clotting was not observed in the whole blood because the fibrin lysed as quickly as it formed (530)

It is worth reemphasizing that in fibrinolytic purpura the concentration of fibrinogen in the plasma is often not sufficiently low to account for bleeding Hemorrhage evidently occurs because the fibrin formed at the sites of injury lyses before hemostasis is achieved Cutaneous ecchymoses or petechiae are not common in fibrinolytic purpura despite its name Severe and often uncontrollable bleeding occurs from operative wounds from the raw placental site from the sites of venepunctures or parenteral injections and rarely from the supposedly intact gastrointestinal tract It is not surprising that the major sites of bleeding should be injured tissues Patients with *congenital* afibrinogenemia may not bleed for months or years In other words even were plasmin to destroy every bit of fibrinogen in the circulating plasma this of itself would not be enough to induce bleeding Bleeding occurs only when the body's hemostatic mechanisms are challenged (540b)

Patients with fibrinolytic purpura may have additional coagulative defects including thrombocytopenia and proaccelerin deficiency the pathogenesis of these changes may be complex Indeed, the mechanisms inducing fibrinolytic purpura are only hazily understood No specific therapy for this syndrome is available except the intravenous injection of human fibrinogen and the replacement of lost blood Treatment with corticosteroids or with the inhibitors of plasmin found in plasma or in soy bean extracts has not yet proved effective

HEMORRHAGIC DISORDERS OF PREGNANCY

Uterine hemorrhage is probably the commonest cause of maternal death during pregnancy or parturition In non fatal cases hemorrhage after delivery is nearly always attributable to uterine atony—that is failure of the uterine musculature to con

tract immediately *post partum*—or to cervical or vaginal lacerations However when uterine bleeding is fatal abnormalities in the blood clotting mechanisms are usually present (545) The commonest change detected is a decrease in the concentration of fibrinogen in the circulating plasma but other hemostatic defects may contribute to the bleeding tendency

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mally rapidly, suggesting that the defibrination is not due to fibrinolysis Moreover, patients with impaired clotting mechanisms may deliver without undue blood loss It is possible that the raw placental site furnishes tissue thromboplastin to clot the blood lost at delivery the defibrinated blood is then expelled Further bleeding is prevented by mechanical occlusion of the myometrial blood vessels by the contracted uterus

Premature Separation of the Placenta Premature separation of the placenta is a common complication of pregnancy occurring in perhaps 0 5 to 1 per cent of cases In a few, the separation of the placenta may be accompanied by serious and even fatal bleeding DeLee in 1901 reported that the uterine bleeding might be associated with a generalized hemorrhagic tendency Dieckmann (170) found that under these circumstances the patient s blood might be hypocoagulable and its fibrinogen content abnormally low This observation has been repeatedly confirmed indeed, in some cases no fibrinogen may be detectable in the circulating plasma In other cases fibrinogen may be present but so altered qualitatively that it reacts poorly with thrombin In addition to hypofibrinogenemia the patient s blood may also be deficient in prothrombin proaccelerin antihemophilic factor and platelets (545 253) Uterine atony, which may accompany premature separation, may add to the patient s hemostatic difficulties

The pathogenesis of the changes in the circulating blood is disputed The concentration of fibrinogen may fall to critical levels within two hours after the onset of premature separation (505), too rapidly to implicate failure in the synthesis of this protein Moloney (442) suggested that fibrinogen is digested by plasma fibrinolytic activity There is no question that fibrinolysis may be present after premature separation of the placenta as in other stressful conditions However evidence that this process is violent enough to contribute appreciably to the bleeding tendency is hard to find A more attractive hypothesis is that the fall in fibrinogen can be accounted for by its loss through hemorrhage and its utilization in the formation of clots at the placental site a view shared by Dieckmann (170) Stouffer and Ashworth (644) and Pritchard (509) Pritchard s quantitative studies suggest strongly that the fibrin lost through uterine bleeding accounts for

the hypofibrinogenemia Still another possibility is that fibrinogen is consumed by widespread coagulation within the mother s blood vessels as the result of inadvertent introduction of the highly thromboplastic placental tissue This hypothesis championed by Schneider (574) Page (477) Weiner (703) and others would account for the multiple coagulation defects observed similar in nature to those of experimental animals injected with tissue thromboplastin (302) However it is unusual to find intra vascular fibrin deposits in the maternal blood vessels at autopsy (575) A fifth possibility proposed by Sharp (590) is that the hemorrhagic disorder is due to an alteration in the coagulability of fibrinogen so that it reacts more slowly than normally to thrombin

The vigor with which the patient with premature separation is treated depends upon her condition The possible value of the transfusion of human fibrinogen must be weighed against the heavy risk of inducing homologous serum jaundice If the patient exhibits no evidence of shock she may be allowed to deliver vaginally without the support of fibrinogen injections In many patients adequate control of bleeding can be obtained through good uterine contraction without the use of fibrinogen (505) Once the uterus has been emptied the concentration of fibrino gen gradually rises to normal levels in the patient who has not been treated with fibrinogen the concentration of this protein reaches the safe level of 150 mg per 100 cc of plasma in eight to twelve hours (505) The platelet count rises more slowly but thrombocytopenia usually plays little or no part in the bleeding tendency

On the other hand if the uterus must be emptied by Cesarean section hypofibrinogenemia should be corrected by the intra venous injection of human fibrinogen An initial dose of 4 gms usually suffices but an additional amount is sometimes needed Fibrinogen is also indicated in the treatment of shock, in addition to the usual measures used to combat this condition

Prior to the introduction of therapeutic fibrinogen the hemor rhagic state associated with premature separation of the placenta was often fatal Now deaths are unusual Pritchard (505) for example observed only one death among eleven cases Unfor

tunately the patient may die of shock or of renal failure despite correction of the abnormality in fibrinogen How to avoid these catastrophes is not clear

Amniotic Fluid Embolism In 1941, Steiner and Lushbaugh (640) delineated a syndrome in which amniotic fluid enters the maternal circulation before, during or after parturition In about one third of such cases the patient has severe respiratory distress and cyanosis and may die within a matter of minutes In the other two thirds no such dramatic episode occurs but the patient gradually slips into shock over a period of several hours Only then may it be realized that she has had severe uterine hemorrhage Prior to the introduction of modern methods of therapy amniotic fluid embolism was often fatal At autopsy both groups of patients are found to have embolization of the maternal circulation by amniotic fluid The diagnosis is established by the presence of lanugo hairs and "squames" that is desquamated fetal epithelium in the maternal pulmonary vessels

Amniotic fluid embolism occurs most frequently in women over the age of thirty particularly multipara and those in whom labor is rapid (545 302 702) Although much is made in published reports of the importance of tumultuous labor in the pathogenesis of amniotic fluid embolism this factor is difficult to evaluate since each author tends to parrot the descriptions of his predecessors

In a review of the clinical features of patients with amniotic fluid embolism Weiner and Reid (702) noted that evidences of a generalized bleeding tendency were common in patients who survived the period of delivery Since amniotic fluid is thromboplastic they hypothesized that it clots the blood within the maternal blood stream and that the bleeding tendency is due to the resultant defibrination of the mother s plasma Following their suggestion, studies of patients with amniotic fluid embolism soon revealed the presence of hypofibrinogenemia (545) In addition other defects of blood clotting have been detected including thrombocytopenia and prolongation of the thrombin and prothrombin times Occasionally excessive fibrinolytic activity is observed the concomitant shock may exaggerate the increased fibrinolytic activity which normally follows parturition The

pathogenesis of these changes in coagulation is unsettled Intra vascular clotting (545 668) the appearance of a heparin like inhibitor (19) and excessive fibrinolysis (19) have all been evoked as responsible for the bleeding tendency, but the evidence supporting each is inadequate

The therapy of amniotic fluid embolism like that of premature separation of the placenta includes the treatment of shock and the replacement of fibrinogen to restore hemostasis the initial does is usually four grams Despite intensive measures the out come may be fatal One of our patients died fifty two hours after delivery despite supposedly adequate therapy This patient s clot ting time remained inexplicably prolonged and she had severe thrombocytopenia She had been transfused with nineteen liters of blood which may have compounded her difficulties (Chapter XXV) In our earlier experience hysterectomy or hysterotomy was performed to control bleeding the results were almost in variably disastrous Now once the surgeon is sure that the uterus has not ruptured patients are treated conservatively with a great improvement in prognosis However in non fatal cases proof of the diagnosis of amniotic fluid embolism is lacking

In a few patients with symptoms suggestive of amniotic fluid embolism a hemorrhagic tendency exists in the absence of signifi cant hypofibrinogenemia (545) Perhaps in some of these patients the bleeding is due to abnormal fibrinolytic activity not detect able in peripheral blood or to some other hemostatic defect Since these patients usually recover the diagnosis of amniotic fluid embolism is usually unproved

The Hemorrhagic Disorder Accompanying Intrauterine Re tention of a Dead Fetus In 1950 Weiner Reid Roby and Dia mond (704) described three cases in which intrauterine death had occurred during the second trimester of pregnancy Spon taneous delivery eight to eleven weeks after fetal death was accompanied by severe uterine bleeding hypofibrinogenemia and in two instances a generalized bleeding tendency These three cases were among fifteen in which delivery of the fetus was delayed Subsequently Pritchard and I (506) observed eight instances of hypofibrinogenemia among thirty-one patients with missed abortion Three of these eight patients were studied only

after bleeding had begun The true incidence of hypofibrinogenemia therefore, was five of twenty eight cases

The cause of fetal death does not seem to be a factor in the pathogenesis of hypofibrinogenemia In most cases, fetal death occurs in the fourth month of pregnancy or thereafter and the bleeding tendency appears three or more weeks later In patients studied prior to delivery the fall in the concentration of fibrinogen is usually gradual In at least one case after the concentration of fibrinogen had fallen to 100 mgm per 100 cc of plasma it stayed at this level for over four weeks when the patient was delivered

The mechanism of hypofibrinogenemia in patients with retained dead fetus is unknown One view that abnormal fibrinolysis destroys the circulating fibrinogen finds no support in studies of peripheral blood either at delivery or during the preceding weeks Extravascular fibrinolysis cannot be excluded Other schools blame intravascular coagulation or impairment of the synthesis of fibrinogen again without proof Another suggestion is that the fibrinogen is present in the plasma in a chemically altered state Though this may well be true the alteration must be so drastic that the fibrinogen cannot be detected either by chemical or electrophoretic analysis

Jackson and his associates (302) have summarized other changes in the clotting mechanisms found in patients in whom a dead fetus is retained Thrombocytopenia prolongation of the one stage prothrombin time and a decrease in the concentration of proaccelerin have all been noted However such changes have not been seen in patients who were studied prior to delivery so that they are probably not a basic part of the syndrome

The bleeding tendency associated with the retention of a dead fetus has a good prognosis although death from shock or lower nephron nephrosis has been described A serious complication of missed abortion fortunately rare is concomitant premature separation of the placenta

Once the diagnosis of retained dead fetus is entertained the patient should be instructed to report to her physician any type of bleeding—gingival cutaneous uterine or otherwise Quantitative determinations of the concentration of fibrinogen in the patient s

plasma should be made at intervals of five to seven days If the concentration of fibrinogen falls below 200 mg per 100 cc the uterus should be emptied When it is less than 150 mg per 100 cc this procedure should be performed only after the intra venous administration of four grams of fibrinogen Labor is not contraindicated once the hypofibrinogenemia has been corrected Within a few hours after the uterus has been emptied the con centration of fibrinogen rises and reaches normal or even supra normal levels within a day

Self induced Abortion Rarely individuals who have attempted to induce abortion upon themselves develop generalized hemor rhagic symptoms The cases do not fit into a uniform pattern since the circumstances attending the abortion and the stage of pregnancy have varied widely Hypofibrinogenemia or afibrino genemia has been present in all the reported cases (123 504 302 113) Severe thrombocytopenia and prolongation of the thrombin time have also been described Bacteremia has been detected in nearly every case the responsible organism has varied from pa tient to patient In one case acute yellow atrophy of the liver may have contributed to the genesis of the clotting abnormalities The mechanisms leading to hypofibrinogenemia in patients with self induced abortion are unknown and may well be different in different cases At autopsy evidences of intravascular coagulation in the small blood vessels of many organs have been described The lesions have been likened to those produced in animals by the intravenous injection of bacterial endotoxins (395) Only occa sionally has abnormal fibrinolytic activity been demonstrated al though it was sought in all (237a) In one patient with bactere- mia due to Clostridium perfringens and a member of the Coli Aerogenes group a violent hemolytic anemia was also present (540a) No fibrinogen was detected in the plasma nor more than traces of antihemophilic factor or proaccelerin the patient s plas ma interfered with the action of thrombin on normal plasma No evidence of fibrinolysis could be found

In the few reported cases therapy has been unsuccessful The administration of fibrinogen transfusions of blood or plasma for the treatment of shock appropriate antibiotics and corticosteroids may be tried

HYPOFIBRINOGENEMIA WITH NEOPLASMS

A generalized bleeding tendency has been described repeatedly in patients with carcinoma of the prostate (323, 653, 407) In such cases, the concentration of fibrinogen in the circulating plasma is usually decreased to abnormally low levels This hypofibrinogenemia may be accompanied by ecchymoses, hematuria sub conjunctival or mucosal hemorrhages gingival bleeding bleeding after surgical procedures as minor as marrow aspiration, and even bleeding into the central nervous system Besides the low fibrinogen levels the clotting time and the bleeding time may be prolonged The one stage prothrombin time is usually long too but this is often only a reflection of the hypofibrinogenemia The tourniquet test may be positive Thrombocytopenia is sometimes present as well as moderate deficiencies of antihemophilic factor proaccelerin prothrombin and the stable serum factors

The pathogenesis of hypofibrinogenemia in carcinoma of the prostate is not understood In nearly every reported case the tumor has metastasized to bone Tagnon (653) and others (628 510) have suggested that fibrinogen is destroyed either by plasmin or by a fibrinolytic enzyme elaborated by prostatic tissue but the evidence supporting this view is not convincing On the other hand Frick (222) and Rapaport (527) could not demonstrate fibrinolytic activity in their cases My own experience is in agreement with their studies An alternative hypothesis that the fibrinogen has been consumed in intravascular clotting has some support (527)

Often the hemorrhagic diathesis does not seem to interfere with the otherwise progressive course of the illness but at times the patient may die of bleeding into the central nervous system Treatment for the acute emergency of bleeding with hypofibrinogenemia consists of the intravenous injection of four grams or more of human fibrinogen repeated whenever needed Remission of hypofibrinogenemia has been reported after treatment with cortisone or estrogens (527) However the hypofibrinogenemia associated with carcinoma of the prostate may vary in intensity from week to week Thus in a case under my care three distinct episodes of hypofibrinogenemia occurred over a period of six weeks each terminated by the intravenous injection of

four grams of human fibrinogen Three months after the first bout of bleeding the patient died of homologous serum jaundice In view of the fluctuating nature of the hypofibrinogenemia the value of the therapeutic agents which have been proposed is uncertain

Rarely hypofibrinogenemia has been observed in association with carcinoma of such other organs as the gall bladder (301) bronchus (216a) pancreas (222 152) or stomach (222 53) particularly linitis plastica (65) Usually bony metastases are demonstrable The pathogenesis of hypofibrinogenemia in these cases is as obscure as in carcinoma of the prostate Biben (65) and Bennike (53) were unable to demonstrate fibrinolysis in the blood of patients with carcinoma of the stomach The wide variety of coagulative defects accompanying carcinoma of the prostate is also found with these other tumors Among six reported cases of hypofibrinogenemia with carcinoma of the stomach thrombocytopenia was present in five (65)

Hypofibrinogenemia has also been described in acute and chronic leukemias and lymphomas of various types (124 497) Again the pathogenesis is obscure Middlebrook (434) demonstrated that intravenously administered fibrinogen disappeared at a more rapid rate than in normal individuals but he was unable to attribute this loss to fibrinolysis

PURPURA FULMINANS

Although the term purpura fulminans has been used to describe many syndromes this ominous name is well reserved for a peculiar catastrophic disease fortunately rare in which areas of skin suddenly become gangrenous Without warning sharply demarcated blue purple areas appear on the skin of the extremities or less commonly the tip of the nose the chin the lobes of the ears the malar region or the palate In a suspected case under our care a small patch appeared on the breast The blue purple areas vary in diameter from a few cm to 15 or 20 cm or more Often they seem symmetrically disposed but they do not follow the recognized distribution of peripheral nerves Over the ensuing day or two the areas turn from blue purple to black and it is soon apparent that these areas are not ecchymotic but are the sites of

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amputation of the gangrenous areas New lesions may appear over a period of several weeks This was the case in the patient with breast gangrene to which I referred

The treatment of purpura fulminans is not clear Kent was able to control bleeding in his patient with afibrinogenemia by the administration of fibrinogen but cortisone was without effect Little (371) believed that heparin arrested the progress of the disease in a patient with repeated episodes of gangrene I believe that a cautious attitude should be taken toward amputation since far less tissue may need removal than at first seems necessary If the patient survives skin grafting after excision of the gangrenous area may be required

HYPOFIBRINOGENEMIA WITH POLYCYTHEMIA

Since the proportion of plasma to cells is decreased in polycythemia the concentration of fibrinogen in whole blood is necessarily decreased as well (78) Compounding this deficiency, the concentration of fibrinogen in the plasma of patients with both primary and secondary polycythemia may be reduced This hypofibrinogenemia may be of great practical importance since it may be present in children with congenital cardiac disease requiring surgery (271) Hypofibrinogenemia may also contribute to the bleeding of polycythemic patients with thrombocythemia (Chapter XVI) Although splenectomy has been said to increase the concentration of fibrinogen in polycythemia vera (45) in ordinary circumstances polycythemia should be treated by more conventional means

MISCELLANEOUS HYPOFIBRINOGENEMIAS

Although this complication has not been described before, afibrinogenemia was recently seen in a patient with Waterhouse-Friderichsen syndrome

A 17 year old girl was admitted to Euclid Glenville Hospital, Euclid Ohio in severe shock About 18 hours before she felt ill and vomited repeatedly Two hours before admission she apparently collapsed and was said by her father to have had an epileptic fit She was brought to the hospital where her blood

dry gangrene of the skin and immediately subjacent areas Bulli may form in these regions In another patient studied at University Hospitals, the gangrenous patches formed grotesque black bands coursing across each mid lower leg On rare occasions the viscera may be affected

The gangrenous patches seem to result from occlusion of the vessels leading into the area The vessels adjacent to the lesions are the site of a necrotizing vasculitis (109 277) and may be plugged with thrombi which give the appearance of platelets (277) Similar changes have been described in major systemic vessels The skin in involved areas may show a loss of epidermis, edema of the dermis and necrosis

The etiology of purpura fulminans is entirely unknown In many cases lesions appear within a few days to a few weeks after the patient has apparently recovered from an acute infectious disease usually of streptococcal origin Other cases have followed the exanthemata, particularly chicken pox (395 643) and possibly measles (328) The nature of the lesions is unknown beyond the obvious inference that the gangrene is due to ischemia of the area as the result of the vasculitis Several authors have suggested that the lesions are reminiscent of the Shwartzman or Arthus phenomena (277 655 371)

The justification for including purpura *fulminans among* the hemorrhagic disorders is not the nature of the cutaneous lesion which is not truly purpuric but because severe coagulative abnormalities and general bleeding may be present Patients may have epistaxes petechiae hematomas splinter hemorrhages of the fingers and toes and other evidences of a systemic hemorrhagic disorder A number of different defects have been noted in the laboratory The clotting and bleeding times may be prolonged In some cases there may be hypofibrinogenemia or afibrinogenemia at the time of the crisis (277 188) In other cases the prothrombin time has been prolonged and low concentrations of proaccelerin *have been observed In some the platelet count* is depressed (643) In one case a cold precipitable protein was detected in the plasma (277)

The course of the illness is variable The patient may die of shock in two or three days or he may survive only to require

302 Jackson D P Hartmann R C and Busby T Fibrinogenopenia complicating pregnancy Clinical and laboratory studies *Obst Gyn* 5 223 1955

545 Ratnoff O D Pritchard J A and Colopy J E Hemorrhagic states during pregnancy *New Eng J Med* 254 63 97 1955

pressure was unobtainable She had a temperature of 100 6° F respirations were 44 per minute and an apical heart rate of 140 per minute There were petechiae on the face and extremities The patient had had a splenectomy for hereditary spherocytosis when she was a child Blood drawn for cross matching failed to clot even upon the addition of thrombin The patient was treated with blood transfusions and the intravenous infusion of fibrinogen corticosteroids and Levophed She expired suddenly about 22 hours after the onset of symptoms Pneumococcus Type XA was cultured from her blood and her throat Autopsy demonstrated severe diffuse hemorrhages of the adrenals with focal necrosis extensive viseral petechiae and hemorrhages petechiae of the scalp and conjunctivae hydrothorax and ascites and recent vascular thrombi in the small vessels of the brain and uterus Despite the previous splenectomy, a spleen weighing 30 grams was found The diagnosis was made of Waterhouse Friderichsen syndrome associated with pneumococcal sepsis (544a)

In this patient no fibrinogen was demonstrable in the plasma The concentrations of antihemophilic factor pro SPCA Stuart factor, proaccelerin prothrombin and plasminogen were decreased and the platelet count was 120 000 The pathogenesis of the afibrinogenemia could not be determined No evidence of increased fibrinolytic activity was demonstrable in any of the blood samples tested The relationship between this syndrome and that of afibrinogenemia with septic abortion (page 97) is not clear

The hypofibrinogenemia which occurs with transfusion reactions and with amyloidosis is discussed in Chapter XXV and XXVI respectively

SELECTED REFERENCES

29 Alexander B Goldstein R Rich L Le Bolloc'h A G Diamond L K and Borges W Congenital afibrinogenemia A study of some basic aspects of coagulation *Blood* 9 843 1954

38 Astrup T The biological significance of fibrinolysis *Lancet* 2 565 1956

256 Ham T H and Curtis F C Plasma fibrinogen response in man Influence of the nutritional state induced hyperpyrexia infectious disease and liver damage *Medicine* 17 413 1938

accelerin The importance of these cases is that they raise the question of whether antihemophilic factor and proaccelerin may arise from a common precursor If this were the case the combined defect might be due to an abnormality of the gene needed to synthesize this substance Perhaps other genes influence the conversion of the precursor to antihemophilic factor or to proaccelerin This hypothesis fits the fact that the titer of antihemophilic factor is normal in severe parahemophilia and the titer of proaccelerin is normal in classic hemophilia

A third combined defect described by Newcomb and his associates (461), resembles that produced by the administration of coumarin like drugs Their patient an adult woman had had abnormal bleeding since childhood including ecchymoses hematemesis melena hematuria menorrhagia bleeding into the central nervous system and bleeding after tonsillectomy Whether any of her relatives had a bleeding tendency was not clear The patient also had several bizarre symptoms and signs including arthralgia splenomegaly and lymphadenopathy Her prothrombin time was very long an abnormality which was due to simultaneous deficiencies of prothrombin pro-SPCA and Stuart factor (461 68a) A deficiency of Christmas factor was also present These changes resembling those following the administration of dicumarol may rarely be seen in individuals ingesting commonplace doses of aspirin but Newcomb believed that the self administration of drugs was not a factor in their patient The administration of Vitamin K_1 was followed only by transient improvement but the transfusion of 500 ml of fresh plasma produced a remission lasting one to two weeks Newcomb and his associates felt that the patient lacked something required for the synthesis of each of the four deficient factors Similar cases have been reported

SELECTED REFERENCES

461 Newcomb T Matter M Conroy L DeMarsh Q B and Finch C A A congenital hemorrhagic diathesis of the prothrombin complex, *Am J Med* 20 798 1956

585 Seibert R H Margolius A Jr and Ratnoff O D Observations on hemophilia parahemophilia and coexistent hemophilia and parahemophilia *J Lab & Clin Med* 52 449 1958

Chapter X

COMBINED HEREDITARY DEFECTS OF COAGULATION

DURING the last few years numerous cases of multiple congenital deficiencies of clotting factors have been described For example, reports of combined deficiencies of antihemophilic and Christmas factors, antihemophilic factor and proaccelerin and prothrombin Christmas factor pro SPCA and Stuart factor have been published That two independent defects could be present by chance in the same individual is too unlikely to explain the existence of several cases of a particular combined defect Such complex cases may mean that a common step is needed in the synthesis of several clotting factors or that one clotting factor is the precursor of another Or conceivably the tests to determine the presence of clotting factors have been vitiated by an unrecognized circulating anticoagulant Finally the possibility must be considered that the combined defects are acquired perhaps as the result of the ingestion of drugs or that the investigators have misinterpreted the results of laboratory studies

There are several reports in the literature of instances in which classic hemophilia and Christmas disease coexist in the same individual However Graham s (243) scepticism concerning the reality of this combination seems reasonable with currently available data On the other hand at least four authentic instances of combined hemophilia and parahemophilia have been observed (585) In these cases, the symptoms resemble those of classic hemophilia the severity of the disorder has varied from patient to patient In three of the four cases the affected individuals were the result of a consanguineous marriage Several of the patients female relatives have had moderate deficiencies of pro-

On the other hand in one hemophiliac observed at University Hospitals of Cleveland the anticoagulant has been a laboratory curiosity, for his disease has remained mild

A great deal of information is available concerning the nature of the anticoagulant in hemophilia but this has not led to a unified hypothesis The anticoagulant inactivates antihemophilic factor specifically other clotting factors are not affected (408) It behaves like a protein and has usually been localized to the gamma globulin fraction of plasma (155) It is relatively stable to heat and cannot be extracted by ether distinguishing it from the anticoagulant which Tocantins believes is responsible for the basic defect in hemophilia With rare exceptions (262) the reported cases have occurred in patients who had been transfused with normal blood plasma or a concentrate of antihemophilic factor (454) This has led to the hypothesis that the circulating anticoagulant is an antibody arising in response to the antihemophilic factor of normal blood—a protein foreign to the hemophiliac Indeed Craddock and Lawrence (128) and many others have reported that anticoagulant plasma contains precipitins against antihemophilic factor However an equally numerous group of investigators deny that precipitins are demonstrable even in cases previously reported as positive (22) Moreover the inactivation of antihemophilic factor by the anticoagulant may require a period of incubation a property as suggestive of enzymatic activity as of antigen antibody reactions (352) Further studies to be referred to in the succeeding paragraphs do not help to settle this issue

The treatment of hemophilia complicated by the presence of a circulating anticoagulant is difficult The transfusion of blood or plasma is usually ineffective in correcting the hemostatic defect but serves only to replace the lost volume of blood The chief weapon left for the treatment of bleeding is the use of local hemostatic agents One severely ill patient at University Hospitals of Cleveland was given a partial exchange transfusion Although the patient survived it is doubtful that this therapy was responsible Treatment with corticosteroids and ACTH has usually not been helpful However the prognosis in hemophilia complicated by circulating anticoagulants is better than one

Chapter XI

CIRCULATING ANTICOAGULANTS

A CIRCULATING anticoagulant is a substance in plasma which delays the clotting of any normal blood to which it is added Circulating anticoagulants have been described at almost every stage of the clotting process and encompass substances with diverse types of activity Their interest to the clinician is twofold circulating anticoagulants may be related to a bleeding tendency and under some circumstances their detection may be an aid in differential diagnosis

Circulating Anticoagulants Directed Against Antihemophilic Factor In at least three different clinical situations the plasma may contain anticoagulant substances which seem to destroy or inactivate antihemophilic factor These circulating anticoagulants may appear in true hemophiliacs in otherwise normal women within several months after delivery, and unrelated to either hemophilia or pregnancy in middle aged or elderly men and women In each of these circumstances the bleeding tendency simulates that of uncomplicated hemophilia No differences have yet been discerned in the circulating anticoagulant found in the three situations

The presence of a circulating anticoagulant in hemophilic plasma was first clearly described by Lawrence and Johnson (353) in a patient who was refractory to transfusion The patient s blood prolonged the clotting of normal blood Since then many similar cases have been described circulating anticoagulants occur in one fifth or more of cases of classic hemophilia (224, 536 408) Nothing about the nature of the bleeding in these cases distinguishes them from severe uncomplicated hemophilia Suspicion that an anticoagulant is present may be aroused by the patient s poor response to transfusion of blood or plasma

(121) Such cases usually occur in patients over the age of fifty, many of whom have seemed otherwise in good health though some have had such diseases as pemphigus rheumatoid arthritis, rheumatic fever or reticulum cell sarcoma Some of these patients had had blood transfusions prior to the appearance of the anticoagulant but in others no incitant has been recognized Both positive and negative tests for precipitins against anti hemophilic factor have been described (676) in three cases I studied the precipitin test was negative Another possible explanation of the action of these anticoagulants is that they are enzymes which can destroy antihemophilic factor The inactivation of antihemophilic factor by the anticoagulant is not instantaneous but takes place over a period of time (71 259) Margolius and I (534) studied the rate at which antihemophilic factor was inactivated by the plasma of a woman in whom a circulating anticoagulant developed *post partum* The destruction occurred at increasing speed as the temperature of the reaction mixture was increased from 0 to 37° C the kinetics of the reaction seemed compatible with an enzymatic mechanism, but the methods used were too crude to permit a firm conclusion Similar observations have been published by Biggs and her associates (68b)

The care of these patients is most difficult None of the many proposed measures appear to influence the titer of the anticoagulant Exceptionally transient benefit has accompanied corticosteroid therapy (362a) Nonetheless the prognosis is usually good although an occasional death has been reported (423) Ultimately after months or years the circulating anticoagulant disappears If the patient is transfused before the anticoagulant disappears its titer may rise temporarily Moreover in the patients in whom anticoagulants have appeared after delivery a subsequent pregnancy may result in exacerbation after a temporary partial remission (219) However in one case the anticoagulant which developed *post partum* gradually disappeared and then did not recur after a subsequent pregnancy (410) Perhaps another pregnancy will see the reappearance of the anticoagulant

Circulating Anticoagulants Directed Against Christmas Factor Several cases of Christmas disease have been described in

would expect, since patients may survive what seems to be un controllable bleeding In time, the anticoagulant may decrease in titer or even become undetectable However, the anticoagulant usually reappears after subsequent blood transfusion, posing a major problem when such patients require surgery or dental ex traction

The circulating anticoagulants which appear in women *post partum* or in certain other non hemophilic patients are indis tinguishable in their characteristics from the type seen in classic hemophilia The presence of these circulating anticoagulants is usually associated with severe bleeding similar to that of hemo-philia The syndrome appears *de novo* with the sudden appear ance of ecchymoses hematomas or other types of bleeding In several patients bleeding into the tongue or the soft tissues of the neck has led to serious or even fatal asphyxia an event for tunately uncommon in uncomplicated hemophilia (402) Orbital bleeding has resulted in blindness Permanent damage to joints is unusual probably because the disorder is not as protracted as hemophilia

Laboratory tests give results identical with those in classic hemophilia complicated by a circulating anticoagulant (122) The clotting time is prolonged and the patient s blood or plasma prolongs the clotting of normal blood The defect resides in the early stages of clotting for the thrombin and prothrombin times are normal and prothrombin consumption and the results of the thromboplastin generation test are abnormal No antihemophilic factor can be demonstrated in the patient s plasma

As in the case of hemophilia the nature of these anticoagulants is not clear The anticoagulant is usually localized to the gamma globulin and is heat stable In women of child bearing age the anticoagulant may be transmitted to the fetus and demonstrated in her newborn infant for as long as four months (219) A preva lent opinion is that these substances are antibodies directed against antihemophilic factor (676) In this view the anticoag ulant which appears in women within a few months after delivery is due to isoimmunization to the infant s antihemophilic factor in a manner similar to erythroblastosis fetalis This hypothesis does not account for cases which are unrelated to pregnancy

In some cases the use of diluted thromboplastin demonstrates a defect not revealed in the ordinary one-stage test Moreover the patient s plasma prolongs the prothrombin time of a normal plasma with which it is mixed

Circulating anticoagulants of this nature are usually associated with systemic lupus erythematosus in which it appears in from 10 to 25 per cent of cases (273 357) In this disorder other hemostatic abnormalities may contribute to the bleeding tendency (page 144) Often other alterations in the serum proteins may be present for example cryoglobulinemia (449), a positive serologic test for syphilis (350) and positive cephalin flocculation and direct antiglobulin (Coombs) tests The anticoagulant is found in the gamma globulin fraction of plasma (454) It may be transmitted transplacentally to the newborn infant, in whose blood it may be detected for several months (220) Although the anticoagulant is often called an antithromboplastin evidence concerning its mode of action is lacking Extensive studies in our laboratory (408) have failed to demonstrate a chemical reaction between tissue thromboplastin and the anticoagulant Moreover the clotting time is often inordinately lengthened compared with the prothrombin time I am unfamiliar with any observation localizing the action of the anticoagulant more sharply

There is some indication that treatment with corticosteroids may sometimes be followed by disappearance of the circulating anticoagulant (426a) However in other cases these drugs have been without benefit Fortunately the symptoms are usually so mild that no therapy is needed

Circulating anticoagulants apparently specifically directed against proaccelerin (290 204) and pro-SPCA (111) have been described

Heparin like Circulating Anticoagulants Heparin is a water soluble complex polysaccharide esterified with sulfuric acid which has potent anticoagulant properties Isolated first from the heart and liver by McLean heparin is found in highest concentration in the capsule of the liver the heart and the lung (104) The heparin like activity of the various tissues parallel their content of mast cells (306 318) which seem to be rich in this substance and may be the site of its synthesis (336)

which the patients have been refractory to transfusion In some of these circulating anticoagulants directed against Christmas factor have been demonstrated (346 625) In one the titer fell over a period of months, only to rise again when the patient was transfused (364) Studies establishing the nature of the anti coagulant in Christmas disease are not as extensive as those in hemophilia Circulating anticoagulants have been detected in about 12 per cent of patients with Christmas disease (408) There is evidence that the anticoagulant inactivates Christmas factor (364) and that this reaction is more readily demonstrable if the patient s plasma is incubated with normal plasma before the mixture is recalcified As in the case of classic hemophilia, the pathogenesis of circulating anticoagulants in Christmas dis ease is unknown (408) The treatment of patients with this com plication is difficult, for the Christmas factor of transfused blood is inactivated by the patient s plasma

A circulating anticoagulant directed against plasma thrombo plastin antecedent has been described (369)

Circulating Anticoagulants Against the Middle Stages of Clot ting In 1952 Conley and Hartmann (119) described two pa tients with systemic lupus erythematosus in whom the one stage prothrombin time was prolonged by a circulating anticoagulant Subsequently many similar cases have been reported but the essential nature of this syndrome is still unexplained Although evidences of a hemorrhagic disorder—ecchymoses hematuria epistaxes hemoptyses bleeding gums menorrhagia and so forth —may be present these symptoms are usually mild or even ab sent (408) Often the diagnosis is suspected only because the prothrombin time is unexpectedly prolonged

Recognition of the presence of an anticoagulant active at the middle stages of clotting is relatively simple The clotting time of whole blood or plasma is usually prolonged and the patient s plasma lengthens the clotting time of normal blood or plasma Although the one stage prothrombin time is usually prolonged no deficiency of the recognized clotting factors can be demonstrated When the one stage prothrombin time is performed with throm boplastin which has been diluted one hundredfold the difference between the patient s plasma and normal plasma is exaggerated

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The anticoagulant action of heparin is apparently complex It appears to interfere with the interaction of fibrinogen and thrombin with the conversion of prothrombin to thrombin by thromboplastin (401) and with the formation of thromboplastic activity in blood (179) These activities are probably related to heparin s strong negative electrical charge This charge allows the heparin to enter into chemical combination with certain of the plasma proteins (318) Heparin is ineffective except in the presence of a co factor associated with plasma albumin (514)

Whether any physiologically significant amount of heparin is normally present in human blood is disputed (466) When heparin is administered intravenously to normal subjects the clotting time the thrombin time and the prothrombin time are all prolonged The effect of the heparin is gradually dissipated perhaps through the action of an enzyme heparinase which has been isolated from the liver (112) The action of heparin can be neutralized more rapidly by the intravenous injection of protamine sulfate (307) or toluidene blue

Experimentally prolonged bleeding is a typical feature of anaphylaxis or of the shock produced by the injection of peptone Considerable evidence has accrued that this abnormal bleeding tendency is due to the appearance of heparin in the peripheral blood (309) In humans hyperheparinemia if it occurs at all is exceedingly rare Dermatologists recognize a variety of syndromes grouped under the name *urticaria pigmentosa* Benign and lethal familial and non familial varieties have been described Common to all is the presence of increased numbers of mast cells in the tissues In the juvenile benign form of the disease the mast cells are found with especial frequency in the corium In the more malignant usually adult type the mast cells may be found in many organs infiltrating in particular the liver spleen and marrow (572) Although these lesions are thought to be rich in heparin purpuric manifestations are rare except in those patients who have systemic manifestations Moreover evidence that the blood contains appreciable amounts of heparin is unconvincing More likely when bleeding occurs in urticaria pigmentosa it is due to some other coagulative abnormality such as thrombocytopenia (55) A few cases have been

reported in which protracted bleeding tendencies have been attributed to the presence of heparin in the circulating blood (408) In these cases a bleeding tendency appeared in child hood or early adult life The clotting time was long and significantly the thrombin time was greatly prolonged Protamine sulfate or toluidene blue neutralized the abnormality *in vitro* and sometimes *in vivo* (279) In some cases these substances were surprisingly without effect when injected into the patient (50 517) In Quick s (517) case it appeared as if the administration of cortisone or freshly frozen plasma was beneficial In a few patients bleeding has appeared only during adult life during the course of systemic lupus erythematosus (201 657)

In most of the reported cases hyperheparinemia is probably responsible for the bleeding tendency However rigid criteria to establish this diagnosis are yet to be met (408)

Circulating anticoagulants interfering with the formation of fibrin which are not heparin like have been described. For example Conley and his associates (120) observed a long thrombin time in patients with severe liver disease in which this abnormality was associated with evidences of a circulating anticoagulant. This anticoagulant was not neutralized by protamine distinguishing it from heparin Similar cases have been described in multiple myeloma (347 221) On the other hand the prolonged thrombin time commonly found in liver disease systemic lupus erythematosus toxemia of pregnancy or multiple myeloma is usually unaccompanied by evidences of a circulating anticoagulant These patients do not have symptoms attributable to this defect (532)

A *circulating anticoagulant directed against fibrinogen* has been described in a case of congenital afibrinogenemia (page 87)

SELECTED REFERENCES

121 Conley C L Rathbun H K Morse W I II and Robinson J E Jr Circulating anticoagulant as a cause of hemorrhagic diathesis in man *Bull Johns Hopkins Hosp* 83 288 1948

220 Frick P G Acquired circulating anticoagulants in systemic "collagen" disease Auto-immune thromboplastin deficiency *Blood* *10* 691 1955

352 Lawrence J S and Craddock, C G Jr Hemophilia The mecha

nism of development and action of an anticoagulant found in two cases *Science 106* 473 1947

676 Verstraete M and Vandenbroucke J Occurrence and mode of action of endogenous circulating anticoagulants *J Lab & Clin Med 48* 673 1956

Chapter VII

THROMBOCYTOPENIA GENERAL CONSIDERATIONS

PLATELETS the smallest of the cellular elements of peripheral blood appear to serve multiple functions in the prevention and control of bleeding Alterations in the number or quality of the circulating platelets may be accompanied by a hemorrhagic tendency but the mechanisms which result in bleeding are obscure No satisfactory hypothesis has been proposed to explain the disturbing fact that bleeding occurs not only in conditions in which too few platelets are present, but also in those in which the number of platelets is excessive

In ordinary blood smears prepared on cover slips and stained with Wright s stain normal platelets are round oval or rod like and vary in size from about 0 5 to 4 microns in diameter They consist of a homogeneous pale blue *hyalomere* in the center of which are deeper blue granules the *chromomere* or *granulomere*, which give the false impression of being nuclear material In living preparations the platelets appear to be small refractile usually spherical bodies which are carried along in the flowing blood Within a few seconds after contact with a foreign surface numerous pseudopods form at the periphery of unstained platelets and the hyalomere spreads thinly The granulomere coalesces to form a central "pseudonucleus" (90) In the absence of anticoagulants the platelets then undergo what has been called viscous metamorphosis (723), that is they stick to one another become swollen disintegrate and lose their identity This process of viscous metamorphosis occurs in all bloods, although it may be slowed in blood deficient in plasma thromboplastin antecedent or Hageman factor (73) Undoubtedly, the properties of platelets

measurable in the test tube are influenced by these successive changes

The platelets arise from pinched off portions of the cytoplasm of megakaryocytes large pale blue cells with large deeply staining nuclei found in and near the blood vessels in the bone marrow, and much less frequently, in other organs particularly lung spleen and in the fetus, liver Observations in animals and patients with thrombocytopenia suggest that the evolution of platelets from the cytoplasm of megakaryocytes takes about four days The stimuli responsible for their production are unknown

The life span of platelets in the normal individual has been studied by various techniques the most satisfactory of which employ platelets labeled by one or another radio active substance Most observers agree that under normal conditions human platelets survive from eight to eleven days after entering the peripheral circulation (13, 358)

The fate of the platelets is obscure Presumably some are continually utilized in the process of hemostasis How superannuated platelets are removed from the blood stream is not clear, nor is it known whether the spleen plays a part in this removal The platelet count rises after splenectomy both in normal individuals and those with a variety of diseases At least four hypotheses have been proposed to account for this effect of splenectomy Perhaps the spleen exerts an inhibitory effect upon the rate of formation of platelets Removal of the spleen would then release the megakaryocytes from inhibition increasing the number of platelets in the circulation A second possibility is that the spleen in some way alters the platelets so that they become susceptible to removal or destruction in some other organ Perhaps the spleen is one of the organs producing antibodies directed against the platelets removal of this organ would then remove a major source of antibodies Finally it is possible that the function of the spleen is to remove platelets from the circulation either at random or after they have been so modified in the spleen or elsewhere that they are susceptible to destruction The results of experiments to determine the role of the spleen have been conflicting and no answer to this important question is at hand

Even the number of platelets in the circulating blood is dis

puted Innumerable techniques of enumeration have been devised each of which is subject to criticism The two most popular in the United States are the indirect method of Dameshek (142) and the direct method of Rees and Ecker (548 108) or one of its modifications In Dameshek s technique the platelets are counted relative to the number of red blood cells in a wet preparation of diluted blood and the absolute number of platelets is then calculated on the basis of the red blood cell count normal human blood contains between 400 000 and 800 000 platelets per cubic millimeter (633) In the direct method capillary or venous blood is diluted in a red blood cell pipette and the platelets are counted in a hemocytometer Usually the platelets are stained with brilliant cresyl blue and counted under a conventional microscope A more satisfactory technique is to lyse the red cells with 1 per cent ammonium oxalate and then count the platelets by phase microscopy as suggested by Brecher and Cronkite (91) Normally the platelet count by one of the direct methods varies from 150 000 to 350 000 averaging about 250 000 The paradox posed by the inconsistency of the two methods is unsolved Recently Fitch (212) suggested that errors in the distribution of platelets caused the relatively high values obtained by the indirect method and that the direct method was the more likely to be correct. Since the enumeration of platelets is a difficult procedure examination of cover slip blood smears is often a more satisfactory method of appraising their numbers for the inexperienced technician

Under physiological conditions the number of platelets in peripheral blood may vary considerably For example in non pregnant adult women the platelet count is lowest on the first day of the menstrual cycle rises rapidly within three to four days and then gradually falls during the last two weeks of the cycle (499) Severe exercise hemorrhage injury and asphyxia may all be followed by an increase in the platelet count (660) The administration of ACTH to normal individuals induces a sharp fall in the platelet count within three hours the number of platelets returning to normal with twenty four hours (351) Similarly the first reaction to a surgical procedure may be thrombocytopenia (660 713) which is then followed by a brisk

thrombocytosis maximal about a week or two postoperatively (9)

A number of different functions have been ascribed to platelets For many years it was thought that platelets were indispensible for the initiation of clotting a view not yet entirely rejected Contact with a foreign surface was thought to disrupt the platelets releasing a thromboplastin similar to that furnished by injured tissue (*445*) In fact, however platelets are only a poor source of thromboplastin Bordet s (*86*) studies at the turn of the century demonstrated that plasma freed from platelets clots in glass tubes in about the same time as whole blood Clotting then, does not require the presence of platelets Nonetheless platelets do serve an important function in blood clotting platelet free plasma remains fluid when it is incubated in silicone coated tubes, but platelet rich plasma clots quickly Analysis of the role of platelets indicate that they speed the evolution of thrombin in shed blood Although thrombocytopenic blood clots in glass tubes as rapidly as normal blood the conversion of prothrombin to thrombin takes place more slowly (31) As a result, such blood may contain large amounts of prothrombin at a time when virtually all of the prothrombin of normal blood would have been "consumed"

Though platelets do not themselves furnish significant amounts of thromboplastin they are apparently needed for the optimal development of thromboplastic activity from its soluble precursors in plasma Thus platelets are required for normal thromboplastin generation" in the test devised by Biggs and Douglas (69) How platelets influence the evolution of thromboplastin is unknown but this property seems to be related to their content of cephalin like compounds (110) particularly phosphatidyl serine, phosphatidyl ethanolamine or both (*660 667, 406*) Indeed, crude mixtures of cephalins prepared from brain (52) or from soy beans (710, 110) accelerate the clotting of platelet deficient plasma increase the rate at which prothrombin is converted to thrombin and substitute for platelets in the thromboplastin generation test Bergsagel and Hougie (54) have suggested that an active substance is formed by the reaction of antihemophilic factor Christmas factor and calcium This product then causes the disruption of platelets which discharge their granules into the

plasma In turn these granules promote the formation of thrombo plastin

Platelets are also required for clot retraction (660) When normal clotted blood remains undisturbed the clot gradually shrinks and its serum is expressed This retraction may reflect a shortening of the strands of fibrin a viewpoint not accepted uni versally (207) The part played by platelets is unexplained (71) Bettex Galland and Luscher (63) have linked clot retraction to the presence in platelets of a contractile protein similar to muscle actomysin but this report is as yet unconfirmed The degree of clot retraction is influenced by many factors besides platelets including the concentration of calcium ions and the presence of an unidentified co factor in plasma

The completeness with which retraction occurs is roughly dependent upon the number of platelets poor clot retraction usually implies the presence of thrombocytopenia However significant impairment of retraction usually does not occur unless the platelet count by the direct method is below 80 000 to 100 000 per cu mm so that good clot retraction does not rule out throm bocytopenia *The extent of retraction is also related to the* hematocrit and to the amount of fibrin in the clotted blood (387) Relatively speaking the lower the hematocrit the more serum can be expressed from a given volume of blood As a result clot retraction will seem to be more efficient in anemic than in normal or polycythemic blood For this reason qualitative tests of clot retraction may be misleading in thrombocytopenia accompanied by severe anemia On the other hand the smaller the amount of fibrin the smaller volume will be occupied by the retracted clot so that hypofibrinogenemic blood will display excessive clot re traction These two effects must be borne in mind in interpreting measures of clot retraction in normal and thrombocytopenic pa tients Relatively simple methods to correct for the influence of the hematocrit are available (303) but there is no easy way to compensate for variations in the amount of fibrin

The physiologic function of clot retraction is mysterious Budtz Olsen (99) believes that retraction is an atavism a carry over from a period in evolutionary development when the ancestral platelets were a major hemostatic device Another more teleologi

cal, view is that the shrinkage of fibrin which is observed in the test tube as retraction draws together the edges of a wound bridged by this protein The importance of clot retraction in the control of bleeding is suggested by studies in patients with one form of thrombocytopathic purpura (page 170) In this hemorrhagic disorder, the platelets are present in normal numbers but clot retraction is impaired The implication that clot retraction is related to hemostasis seems unavoidable

A third function of platelets related to the maintenance of the integrity of small blood vessels is revealed clinically by studies of patients with thrombocytopenia In such individuals the bleeding time is often abnormally long and tests for capillary fragility give abnormal results The usual interpretation of these observations is that platelets are required to preserve the continuity of small blood vessels An alternate hypothesis must also be considered namely that the same agent which produces thrombocytopenia can injure the vascular wall However, there is experimental evidence that the platelets themselves act locally Direct microscopic observation of the smallest blood vessels in living preparations of the rat s mesentery or the hamster s cheek pouch demonstrate that platelets pile up at the site of vascular injury, and may completely occlude the vessel Perhaps this is the way in which bleeding is controlled when the skin is punctured Zucker (728) observed a concomitant constriction of the blood vessels, an effect she attributed to the release of serotonin from the platelets In the human the small blood vessels at the base of the finger nails seem to constrict when they are injured a phenomenon not seen in patients with thrombocytopenia (388) Such experiments support the view that platelets may help to control bleeding from small vessels

Many other functions have been attributed to the platelets For example normal platelets have properties closely resembling those of proaccelerin (693) and of antihemophilic factor (404) However, platelets have the capacity to adsorb many substances from the surrounding medium Among the substances found in platelets are proaccelerin (288) antihemophilic factor (28) serotonin (728) histamine adenosine triphosphate (87) and epinephrine (701) Considerable doubt exists that any of these substances influences the function of platelets within the circulation

THROMBOCYTOPENIC STATES

The clinical picture which accompanies depression of the num ber of circulating platelets is relatively uniform The patient him self is often aware of the two types of skin lesions which may be present—petechiae and ecchymoses Petechiae are most apt to be observed in dependent areas in the folds of the skin at the knee or elbow and in areas overlying such bony structures as the knees elbows and tibiae They are also numerous at areas where the skin has been compressed by clothing or distal to the site of constriction of an extremity produced for example by garters Sometimes in severe thrombocytopenia purpura the arms or legs are peppered by petechiae A coughing spell may induce a shower of petechiae on the neck face and conjunctivae presumably by increasing the venous pressure The petechiae are usually not palpable but in severe cases they may be raised and indurated Wintrobe (715) emphasized that the petechiae are not associated with erythema or inflamation as in anaphylactoid purpura The site of petechial bleeding is probably at the arterial end of the capillary loop (294)

Ecchymoses are especially likely to occur on the extremities although no part of the body is exempt They differ in no obvious way from the ecchymoses which follow injury in normal indi viduals and the patient will often assume that such injuries have occurred However he may be unable to recall the traumatic in cident and in this way gradually becomes aware of the spon taneous origin of the bruises

The bleeding tendency may be manifest at many sites Petechiae are often present on the oral mucous membranes In severe cases small hemorrhagic blisters appear on the mucous membrane of the lips mouth pharynx and nose Expistaxes gingival bleeding bleeding from the gastrointestinal tract and hematuria are all relatively common in severe cases Gross bleeding from the gastro intestinal tract may reflect the presence of coincidental lesions Menorrhagia is often the first symptom of which the patient is aware vaginal bleeding seems especially frequent in patients with pre existing gynecologic disease Bleeding into the central nerv ous system is common in patients with the profound thrombo cytopenias observed in acute leukemia and aplastic anemia but is

relatively rare in idiopathic thrombocytopenic purpura Its results may be catastropic cerebral hemorrhage is one of the chief causes of death in patients with this syndrome Hemarthroses are conspicuously absent in patients with thrombocytopenia and hematomas of soft tissue so characteristic of hemophilia, are unusual

The diagnosis of thrombocytopenic purpura rests with finding a decreased number of platelets in the peripheral blood The lower limit of normal by the direct method is about 150 000 platelets per cu mm but purpuric manifestations are usually not seen unless the platelet count is less than 100 000 per cu mm Since reliable platelet counts are not always available a well stained blood smear prepared by the cover slip technique should always be examined to confirm the diagnosis When the platelet count is less than 80 000 per cu mm or thereabouts the prothrombin content of serum is abnormally high that is prothrombin consumption is poor In addition clot retraction is usually impaired and the bleeding time may be prolonged In many patients the tourniquet test is positive but the results of this test are often erratic no abnormality may be found in patients whose platelet counts are as low as 10 000 per cu mm

The prognosis of thrombocytopenic purpura is related to

TABLE IV

A TENTATIVE CLASSIFICATION OF THE CAUSES OF THROMBOCYTOPENIA

I Disorders in Which Production of Platelets Is Probably Reduced (Chapter XIII)

A Hypoplasia or Aplasia of Megakaryocytes

1 Cases due to ionizing radiations
2 Cases due to drugs and toxic chemicals (Table V)
3 Congenital hypoplastic anemia
4 Fanconi s Familial Anemia
5 Congenital thrombocytopenia with absent radii
6 Aplastic anemia with thymoma
7 Agnogenic myeloid metaplasia
8 "Idiopathic"

B Infiltration of Marrow by Abnormal Cells

1 Leukemia
2 Metastatic Carcinoma
3 Multiple Myeloma
4 The Histiocytoses

TABLE IV (Continued)

C. Megaloblastic Anemia

D Metabolic Disorders

1 Azotemia
2 Hypothyroidism

E Infections (Table VII)

II Disorders in Which the Life Span of Platelets Is Probably Decreased (Chapter XIV)

A Diseases in Which an Immune Mechanism May Play a Role
1 Sensitivity to drugs (Table VI)
2 Experimental Anaphylaxis
3 Infections (Table VII)
4 Hemolytic anemias (acute idiopathic hemolytic anemia toxemia of pregnancy incompatible transfusion reactions)
5 Systemic lupus erythematosus
6 Thrombotic thrombocytopenic purpura
7 Idiopathic thrombocytopenic purpura

B Diseases in Which Platelets Are Sequestered or Utilized at an Excessive Rate
1 Splenomegaly (e g congestive splenomegaly Gauchers disease sarcoidosis miliary tuberculosis)
2 Sequestration of platelets (e g congenital hemangiomatosis Kaposis sarcoma experimental hypothermia)
3 Intravascular coagulation amniotic fluid embolism (Chapter IX)

C Leukemia and Carcinoma with Adequate Numbers of Megakaryocytes Present in the Marrow (Chapter XIII)

III Thrombocytopenia Due to Dilution of the Platelets by the Transfusion of Platelet Poor Blood (Chapter XXV)

IV Disorders in Which the Pathogenesis of Thrombocytopenia Is Unknown (Chapter XV)

A Infections (Table VII)
B Congenital thrombocytopenia with eczema and repeated infections
C Familial thrombocytopenia
D Onyalai
E Thermal burns
F Heat Stroke
G Kwashiorkor
H Macroglobulinemia (Chapter XXIV)
I Hypofibrinogenemia with carcinoma, premature separation of the placenta etc (Chapter IX)
J Paroxysmal nocturnal hemoglobinuria (Chapter XIV)

several factors including the cause of the thrombocytopenia and the degree of depression of the platelet count Death attributable directly to thrombocytopenia is due either to the loss of blood itself, particularly from the nose or vagina or from bleeding into a vital area, most often the brain However severe thrombocytopenia may be present for many months or years without serious consequences, so that it is difficult to venture a prognostic opinion based solely on the platelet count

Any meaningful classification of the diseases accompanied by thrombocytopenia founders on our inadequate knowledge of the pathogenesis of this syndrome Table IV modified from Harrington s (264) classification divides thrombocytopenic states into those due largely to decreased production of platelets, those in which the life span of platelets is shorter than in normal individuals those in which the platelets are diluted by platelet poor blood and those in which information concerning the mechanism responsible for thrombocytopenia is scanty This classification must not be taken literally since little is known of the mechanisms which result in thrombocytopenia Studies in patients with idiopathic thrombocytopenic purpura which suggest with equal force that decreased production and increased destruction of platelets may occur demonstrate the difficulties inherent in present day nosology

Determination of the cause of thrombocytopenia must be based on thorough and often protracted study In eliciting the patient s history inquiry must be made concerning possible exposure to irradiation or to a drug or chemical agent which might be responsible for his thrombocytopenia He should be questioned about the presence of other manifestations of some systemic disease in which thrombocytopenia may occur Rarely a familial history of bleeding may point to a diagnosis of one of the congenital thrombocytopenias Physical examination may reveal enlargement of the lymph nodes suggestive of lymphomatous or granulomatous disease The spleen may be palpable thrombocytopenia may accompany splenomegaly caused by many different lesions Characteristic rashes may suggest such diagnosis as systemic lupus erythematosus congenital hemangiomatosis Gaucher s disease or Kaposi s sarcoma

Examination of bone marrow obtained by aspiration is impor tant in order to determine the cause of thrombocytopenia and to provide information helpful in deciding whether splenectomy should be used as a therapeutic procedure The marrow is studied with two general purposes in view The aspirate may demonstrate abnormalities which point to a definitive diagnosis For example the marrow may indicate the presence of leukemia or may be infiltrated with metastatic carcinomatous cells or cells typical of such disturbances as Gaucher s disease

In other cases no abnormal cells may be seen in the marrow In this event a careful examination should be made for the presence and character of the megakaryocytes Sometimes as in aplastic anemia these cells may be virtually absent from the marrow Under other circumstances the megakaryocytes may be present but possess less cytoplasm than normally and give no in dications that platelets are being formed Such cells often described as quiescent are common in idiopathic thrombocytopenic purpura or in the purpura accompanying systemic lupus erythematosus miliary tuberculosis or sensitivity to certain drugs Megakaryocytes with this appearance are not necessarily dam aged nor indeed quiescent for as Craddock (126) emphasized these alterations are seen under conditions which suggest that these cells may be producing platelets as rapidly as their rate of maturation permits These "quiescent" megakaryocytes must be distinguished from osteoclasts whose nuclei are usually multiple The presence of megakaryocytes is important to establish since therapeutic splenectomy is much less successful when the marrow lacks these cells

Finally in patients with agnogenic myeloid metaplasia myelofibrosis aplastic anemia or the early stages of leukemia no mar row may be obtained by aspiration When this occurs surgical biopsy of the marrow should be performed in an effort to make a definitive diagnosis

Other diagnostic tests may be suggested by the particular problem at hand For example in patients in whom the cause of the thrombocytopenia has not been established reticulocytosis may lead to the diagnosis of a hemolytic disorder or a positive L E test may indicate the presence of systemic lupus erythematosus

SELECTED REFERENCES

99 Budtz Olsen O E *Clot Retraction* Oxford Blackwell Scientific Publications 1951
358 Leeksma C H W and Cohen J A Determination of the life span of human blood platelets using labeled diisopropyl fluorophosphonate *J Clin Invest* *35* 964 1956
660 Tocantins L M The mammalian blood platelet in health and disease *Medicine* *17* 155 1938

Chapter XIII

THROMBOCYTOPENIA DUE TO UNDERPRODUCTION OF PLATELETS

IN all probability, more cases of thrombocytopenia are due to underproduction of platelets than to excessively rapid destruction or consumption of these cells (217) Thrombocytopenia is a constant feature of hypoplastic or aplastic anemia of whatever cause in these patients the marrow does not produce adequate numbers of red cells white cells or platelets Impaired formation of platelets is also observed in patients in whom the marrow is crowded with abnormal cells or is depressed by nutritional deficiency metabolic abnormalities or infection

Thrombocytopenia with Hypoplastic or Aplastic Anemia The thrombocytopenia associated with hypoplastic or aplastic anemia is best exemplified by cases resulting from exposure to ionizing irradiation Experimental (132) and clinical (587) experience indicates that a hemorrhagic state may follow irradiation of the marrow to a degree just short of that which would be lethal within a few days A week or less after a single exposure to x rays a bleeding tendency appears which may soon become of dominant importance Simultaneously severe thrombocytopenia and its laboratory concomitants become manifest The thrombocytopenia is apparently caused by destruction of the megakaryocytes of the marrow The life span of those platelets already in the circulating blood is unimpaired so that the onset of thrombocytopenia is delayed until the destruction or removal of the surviving platelets (551) Patients who have been exposed to damaging amounts of irradiation have leukopenia and if they survive for several weeks evidences of aplastic anemia so that therapy of the purpura is only one of the problems requiring solution

Thrombocytopenia due to decreased production of platelets may also result from the action of drugs which depress the activity of bone marrow (Table V) The depressing effect of some such as benzol and many of its derivatives, the nitrogen mustards myleran, urethane, the antagonists of folic acid and other oncolytic agents is a regular feature of their biological activity and is

TABLE V

CHEMICAL AGENTS WHICH MAY PRODUCE THROMBOCYTOPENIA BY DEPRESSING THE PRODUCTION OF PLATELETS*

1	*Oncolytic compounds* Nitrogen mustard and related compounds urethane myleran folic acid antagonists 6 mercaptopurine
2	*Organic solvents* Benzene and related compounds petroleum distillates naphtha Stoddard s solvent
3	*Chemotherapeutic agents* Arsphenamine and other organic arsenicals sulfonamides (including acetazolamide) quinacrine para amino salicylic acid (?)
4	*Antibiotics* Chloramphenicol chlortetracycline oxytetracycline streptomycin, ristocetin penicillin (?)
5	*Anticonvulsants* Mesantoin tridione phenurone etc
6	*Antihistaminics* Pyribenzamine phenindamine
7	*Sedatives* Barbiturates
8	*Tranquilizers* Meprobamate promazine (?) chlorpromazine (?)
10	*Heavy metals* Gold bismuth silver mercury lead
11	*Hair dyes stove and shoe polishes*
12	*Insecticides* D D T hexachlorocyclohexane chlordane (?)
13	*Anti Thyroid drugs* Methimazole carbimazole propylthiouracil (?)
14	*Anti Diabetic drugs* Carbutamide
15	*Miscellaneous* Dinitrophenol, trinitrotoluol, dinitrobenzene naphthalene nitrous oxide anesthesia hydralazine hydroquinone creosote colchicine probenecid (?) digitoxin (?) estrogens (?)

* Modified from Harrington (264) and Scott (580)

not dependent upon idiosyncracy of the exposed individuals (160) Given a large enough dose and sufficient time nearly everyone will succumb to these agents Other drugs such as chloramphenicol (608) organic arsenical or gold compounds or anti convulsant drugs (580) depress the marrow only in an occasional patient Although these drugs are said to produce idiosyncratic reactions their mode of action seems to differ fundamentally from that of such drugs as quinine or Sedormid which induce thrombocytopenia via an immunologic mechanism Perhaps as Scott Cartwright and Wintrobe (580) have speculated affected

individuals may have some fundamental biological defect which increases their susceptibility to the drug When thrombocytopenia results from the depressant effect of drugs upon the marrow leukopenia and if the effect of the agent is sufficiently protracted aregenerative anemia are usually present

Often the cause of hypoplastic or aplastic anemia cannot be determined It is probably that these cases do not form a single group but that several disease processes have as their end result general depression of bone marrow activity Rarely aplastic anemia complicates severe infections such as tuberculosis bacterial endocarditis or brucellosis (580) Rarely too aplastic anemia may arise from a genetic defect Several children within a family may have anemia leukopenia and thrombocytopenia (555) These children may survive for eight to ten years before they succumb to the disease Thrombocytopenia also forms part of the aplastic anemia of patients with Fanconi s anemia (155) In this familial disorder of children probably inherited as a recessive trait aplastic anemia is combined with other congenital anomalies including cutaneous pigmentation the absence of digits congenital anomalies of the urinary tract dwarfism microcephaly deafness or congenital heart disease Boys are more frequently affected than girls (155) The bone marrow is hypoplastic The aregenerative nature of the anemia was demonstrated by Reinhold (530) who showed that red cell survival was normal in this disease Aplastic anemia and its concomitants usually make their appearance when the patient is four to twelve years old the disease is usually fatal by the mid teens The results of splenectomy are unpredictable the operation occasionally producing a remission of the anemia

With great rarity thrombocytopenia without anemia may occur in newborn infants as a familial trait in association with congenital anomalies (274) In such infants the radii are usually absent and there may be other skeletal defects and cardiac anomalies It is probable that *the thrombocytopenia is due to underproduction of* platelets for no megakaryocytes are seen in aspirated bone marrow (192) Most patients die in infancy sometimes as the result of bleeding an occasional individual survives into the teens The pathogenesis of the disorder is unknown but its occurrence in

siblings suggests that it is an inherited defect (591) No treatment is available splenectomy has been without benefit

Attention has also been directed recently to the relationship between thymoma and aplastic anemia In at least six reported cases thrombocytopenia has accompanied the anemia and leukopenia The disease occurs in both sexes in patients ranging in age from 20 to 76 years (320)

In the great bulk of patients with aplastic or aregenerative anemia the disease appears to arise *de novo* (580) In all the decrease in the number of circulating platelets is apparently due to a decrease in the rate at which they are formed Normal platelets transfused for the first time into patients with this disease seem to survive a normal time (286) There is no evidence that an excessive rate of destruction, such as occurs in idiopathic thrombocytopenic purpura, is responsible for the thrombocytopenia

The clinical picture of aregenerative anemia is the same whatever its cause The first symptoms are most often referable to the thrombocytopenia less often to the anemia and only rarely to the granulocytopenia (580) Patients in whom purpura is prominent have the usual galaxy of epistaxes gingival bleeding petechiae ecchymoses hematuria and menorrhagia In severely affected cases there may be gastrointestinal or central nervous system hemorrhages the commonest immediate cause of death (580) The patient s life may also be imperiled by agranulocytic angina or other infections presumably because leukopenia is present Progressive weakness dyspnea and perhaps edema may reflect the patient s anemia

The bone marrow in hypoplastic or aplastic anemia is nearly always hypocellular and megakaryocytes are rare or absent in aspirated marrow Those megakaryocytes which may be seen are often grossly abnormal in appearance Occasionally as Bomford and Rhodes (81) pointed out the aspirated marrow may be normally cellular or even hypercellular but even in such cases usually few or no megakaryocytes are to be found The marrow may be fatty and fibrosed Accurate diagnosis requires that a surgical biopsy specimen be obtained in every instance for in cases of aleukemic leukemia aspirated marrow may be indistinguishable from that of aplastic anemia (683)

The treatment of thrombocytopenia associated with depression of the bone marrow is unsatisfactory Exposure to any possible offending agents must be discontinued Although one may relieve the anemia by the transfusion of blood this procedure does not ordinarily alter the peripheral platelet count The transfusion of polycythemic blood rich in platelets may raise the number of circulating platelets for a few days but the platelet count soon falls (630) The blood should be freshly drawn preferably into plastic bags and with great care to prevent injury to the platelets (227) Subsequent transfusions of platelet rich blood or plasma are progressively less effective their benefit seems to be vitiated by the development of anti platelet antibodies (634 630) Many attempts have been made to prepare concentrates of platelets but the benefit which they provide is transitory at best and can do no more than tide the patient over a crisis Occasionally a patient will respond to treatment with corticosteroids but in general this is a disappointing procedure (580 635) A few cases have responded to splenectomy used as a desperate measure in patients with severe bleeding but ordinarily this procedure is also without benefit (580) Wintrobe (715) believes that splenectomy is successful only in cases in which the marrow is not completely aplastic This procedure has been disappointing in the aplastic anemia related to irradiation drug intoxication Fanconi s anemia or thymoma Thymectomy has been equally disappointing in those cases associated with thymoma

The prognosis of aplastic anemia is not as grave as it was some years ago since life may be sustained by the transfusion of blood and by treatment of infections as they arise and an occasional case may respond to splenectomy (580) However these measures will not protect the thrombocytopenic patient against a lethal hemorrhagic accident It is noteworthy that in two recent series complete or partial remissions occurred in three of eighteen (155) and fourteen of thirty nine (580) patients In the latter series nine of the patients in whom remission occurred had been treated by splenectomy The belief that remission is more likely to occur in cases in which a causative agent has been identified (715) is not borne out in Scott s excellent study (580) Complications of therapy such as hemosiderosis (441) and homologous serum

jaundice, sequelae of the innumerable transfusions to which these patients are subjected, occasionally affect the course of the illness adversely

Thrombocytopenia Associated with the Infiltration of Marrow by Abnormal Cells Thrombocytopenia which seems to result from impaired production of platelets is found in a number of conditions in which the marrow is crowded by abnormal cells (379) The thrombocytopenia of patients with leukemia is probably the commonest example This defect is prominent in acute leukemia most cases of chronic lymphatic leukemia and some of advanced chronic myeloid leukemia Bleeding is often the first and most disturbing symptom of patients with acute leukemia In many cases examination of the marrow will demonstrate that it is crowded with tumor cells and that megakaryocytes are scarce or absent Occasionally however the marrow is not infiltrated densely enough to support a mechanical explanation for the absence of megakaryocytes raising the question whether mere crowding of the marrow is ultimately responsible for the thrombocytopenia Indeed in chronic lymphatic leukemia the peripheral platelet count may fall without a significant change in the appearance of the marrow (517)

Infiltration of the marrow has also been implicated in the thrombocytopenia which occasionally complicates carcinoma Jarcho (310) pointed out that the combination of carcinoma and thrombocytopenic purpura occurs most often in individuals under the age of forty In his experience the commonest neoplasm was carcinoma of the stomach a lesion which was often unsuspected prior to autopsy Jarcho believed that thrombocytopenia is particularly frequent when there is lymphangitic spread of the carcinoma The marrow is damaged not only by the invading tumor cells but by the accompanying hemorrhage and fibrosis as well Nonetheless cases are occasionally observed in which carcinoma is accompanied by thrombocytopenic purpura in the absence of demonstrable bony metastases and the relationship between the two lesions remains obscure (660 565) It is noteworthy that in patients with carcinoma and thrombocytopenia, immature red cells and white cells are common in the peripheral blood there may be evidences of extramedullary hematopoiesis and hypofibrinogenemia may be present (222)

In other disorders in which the marrow is infiltrated with abnormal cells the suggestion has been made that thrombocytopenia is due to destruction of functional megakaryocytes Crowding of the marrow by abnormal cells has been evoked as the cause of some instances of thrombocytopenia associated with Gauchers disease Niemann Picks disease and Hand Schuller Christian syndrome The evidence supporting this interpretation is meager On the contrary de Vries and Izak (164) have emphasized that the thrombocytopenia in Gauchers disease need not be accompanied by crowding of the marrow with abnormal cells Again the pathogenesis of thrombocytopenia in multiple myeloma is unclear although the number of megakaryocytes in the marrow is usually decreased (305) One wonders whether the abnormal viscous plasma proteins characteristic of this disease interfere with the nutrition of the marrow

The thrombocytopenia caused by the infiltration of the marrow by abnormal cells is often refractory In patients with leukemia who respond to therapy with irradiation or oncolytic agents a rise in the platelet count may accompany improvement in other modalities but often the thrombocytopenia is intensified by the treatment itself Corticosteroids may reduce the bleeding manifestations but ordinarily do not alter the platelet count (635) When the marrow of patients with leukemia or carcinoma is not infiltrated with tumor cells and contains adequate numbers of megakaryocytes the platelet count may rise after splenectomy Possibly in these cases thrombocytopenia is the result of accelerated destruction of platelets Similarly in Gauchers disease the thrombocytopenia usually responds to splenectomy

Under most circumstances the prognosis of thrombocytopenia in which the marrow is infiltrated by abnormal cells is that of the underlying disorder but particularly in leukemia death may come from hemorrhage into the brain gastrointestinal tract or elsewhere

Thrombocytopenia with Megaloblastic Anemia Occasionally thrombocytopenia accompanies the megaloblastic anemias (660 363 144) A tempting assumption is that patients with these anemias lack a nutriment required for the maturation of platelets —Vitamin B_{12} in pernicious anemia and folic acid in the megaloblastic anemias of pregnancy sprue and infancy Whether

these mechanisms are actually responsible is not clear but a re mission of thrombocytopenia follows treatment of the primary disorder Only rarely is thrombocytopenic purpura an important part of the clinical picture bleeding in patients with sprue is much more likely to be due to a deficiency of Vitamin K depend ent clotting factors

Thrombocytopenia with Metabolic Disorders and Infections Thrombocytopenia due to impaired production of platelets has also been ascribed to the presence of certain metabolic disorders The low platelet count which accompanies azotemia (565) and hypothyroidism (471) has been attributed to this mechanism The thrombocytopenia which occurs at the height of certain acute infectious diseases may also be due to depressed activity of the bone marrow These disorders are discussed on page 139

SELECTED REFERENCES

81 Bomford R R and Rhoads C P Refractory anaemia I Clinical and pathological aspects *Q J Med n.s 10* 175 1941

155 Dawson J P Congenital pancytopenia associated with multiple congenital anomalies (Fanconi type) Review of the literature and report of a 20 year-old female with a 10 year follow up and apparently good response to splenectomy *Ped 15* 325 1955

302 Josse J W and Zacks S I Thymoma and pancytopenia Report of a case and review of the literature *New Eng J Med 259* 113 1958

580 Scott J L Cartwright G E and Wintrobe M M Acquired aplastic anemia An analysis of 39 cases and review of the per tinent literature *Medicine 38* 119 1959

587 Selling L and Osgood E The Action of Benzol Roentgen Rays and Radioactive Substances on the Blood and Blood forming Tissues in *Handbook of Hematology* H Downey edit New York P B Hoeber Inc *4* 2693 1938

Chapter XIV

THROMBOCYTOPENIA IN WHICH THE LIFE-SPAN OF PLATELETS IS DECREASED

DISEASES IN WHICH AN IMMUNE MECHANISM MAY PLAY A ROLE

IN SEVERAL circumstances thrombocytopenia seems to be due to a decrease in the life-span of platelets as the result of an immune reaction Experimentally thrombocytopenia is readily induced by the injection of heterologous antiplatelet serum (362 569) In human beings a similar phenomenon may explain the development of refractoriness to the transfusion of platelet rich blood in the treatment of aplastic anemia In other cases thrombocytopenia may be associated with antigen antibody reactions in which the platelets are only incidentally involved. The thrombocytopenia associated with sensitivity to drugs is the clearest example of this phenomenon Similar mechanisms may be responsible for the decrease in the platelet count found in many infectious diseases, acute hemolytic anemias systemic lupus erythematosus thrombotic thrombocytopenic purpura toxemia of pregnancy and indeed idiopathic thrombocytopenic purpura The data linking thrombocytopenia to hypersensitivity in each of these disorders vary in the degree of conviction they carry

The confusion which surrounds the problem of relating thrombocytopenia to an immune reaction is exemplified by studies of anaphylactic shock in experimental animals (2) This phenomenon is accompanied by a sudden decrease in the number of circulating platelets which may contribute to the hemorrhagic nature of anaphylactic lesions However the thrombocytopenia is not necessarily of immunologic origin since it is seen in experi

mental shock induced by the intravenous injection of peptone Perhaps then the fall in the platelet count in anaphylaxis is only an aftermath of the antigen antibody reaction Similar difficulties arise in attempts to unravel the course of events in the various clinical situations in which the platelet count is depressed

Thrombocytopenia Due to Sensitivity to Drugs Sensitivity to drugs is an uncommon but highly illuminating cause of thrombo cytopenic purpura The number of circulating platelets falls pre-

TABLE VI

CHEMICAL AGENTS WHICH MAY PRODUCE THROMBOCYTOPENIA VIA AN IMMUNE MECHANISM*

1	*Sedatives* Sedormid and related carbamides phenobarbital dormison, reserpine (?)
2	*Antipyretics* Aminopyrine salicylates
3	*Chemotherapeutic agents* Quinine sulfonamides (including acetazolamide) organic arsenical compounds (sulfarsphenamine arsphenamine neoarsphenamine) para amino salicylic acid chrysarobin fuadin
4	*Cardiac Therapeutic agents* Quinidine chlorothiazide hydrochlorothiazide digitoxin (?)
5	*Antihistaminics* Chlortrimeton benadryl antazoline
6	*Anti Diabetic drug* Chlorpropamide
7	*Miscellaneous* Ginseng (Chinese medicinal tea) phenolphthalein whooping cough vaccine (?)

* Modified from Harrington (264)

cipitously soon after the patient is given a drug which has been administered previously In other instances the thrombocyto penia begins after a week or more of continual therapy with a drug which the patient may have taken for the first time Other evidences of an allergic reaction including chill fever, gastro intestinal distress urticaria asthma rhinitis and rash may be present the spleen is sometimes palpable The sensitivity to a particular drug may be highly specific so that a patient will develop thrombocytopenia after the administration of quinine but not quinidine its optical isomer or *vice versa*

A long list of drugs has been said to produce thrombocytopenia in the sensitized individual (Table VI) The allergic nature of these drug purpuras has been suspected for many years Over thirty years ago, Rosenthal (565) demonstrated that the intra

dermal injection of quinine produced thrombocytopenia in a sensitized individual Posner (503) suspected that the fall in platelets is due to a circulating agent which acts only in the presence of the drug for a mother and her newborn infant both developed thrombocytopenia after quinine was used to induce labor He postulated that a thrombocytopenia producing substance crossed the placenta from mother to infant Ackroyd (3 4 6 8) in a perceptive series of experiments showed that in the presence of the responsible agent the serum of a patient with drug purpura damaged platelets *in vitro* The combination of the drug Sedormid and the patient s serum agglutinated normal platelets impaired clot retraction and in the presence of complement lysed the platelets complement was "fixed" in the reaction Ackroyd assumed that Sedormid combined with the platelets to form a complete antigen which evoked the production of antibodies When the drug was readministered to the sensitized patient it combined with his platelets and the combination then reacted with antibody damaging the platelets

Bolton (60) on the basis of a study of quinidine induced thrombocytopenia raised doubts concerning this simple explanation for a firm union between drug and platelets was not demonstrable An alternative hypothesis has been suggested by Shulman (595) He believes that the drug in combination with a plasma protein may be the antigen to which the patient becomes sensitive When the drug is readministered to the sensitized patient, it reacts with antibodies previously formed against it and this complex is then adsorbed by the platelets In this process the platelets are not destroyed but are so altered that they are removed from the circulation prematurely

These experimental observations help to explain some of the clinical characteristics of these drug induced purpuras First normal numbers of megakaryocytes are ordinarily present although they are not surrounded by nascent platelets (77) Secondly when the administration of the offending drug is discontinued the rise in the platelet count may not occur for several days that is until the drug has been excreted or metabolized and time has elapsed for the platelets to regenerate Thirdly since hemorrhagic phenomona cease before a significant rise in the

platelet count, it is possible that the first platelets formed are used for hemostasis and the platelet count will not return to normal levels until a surplus accumulates

In this description of the drug induced purpuras, I have em phasized the thrombocytopenia Ackroyd wondered whether a drug responsible for a fall in the platelet count might not also produce endothelial damage This hypothesis implies that drug and endothelial tissue combine to form an antigen The antibody which develops against this complex then produces endothelial damage when the drug is readministered If the offending drug was applied to the skin of a sensitive patient, petechiae appeared at the site of the test Ackroyd interpreted this observation as evidence of capillary damage He felt that this hypothesis helped to explain those cases in which purpura occurs without throm bocytopenia Although Bolton and Shulman could not demon strate a reaction between quinidine vascular tissue and the serum of a sensitive patient the possibility exists that sensitivity to an endothelial drug complex may result in non thrombocytopenic purpura Certainly, idiosyncrasy to drugs may occur without demonstrable abnormalities in the circulating blood (Chapter XXII) In one case the offending agent was acetylbromdiethyl acetylcarbamide (Sedamyl) chemically a close relative to Se dormid In this patient wide spread petechiae and ecchymoses followed the ingestion of the sedative but thrombocytopenia was not demonstrable at a time when fresh cutaneous lesions were present

The possibility that purpura is due to sensitivity to drugs should be entertained in all patients whether or not thrombocytopenia is present Before splenectomy is performed for so called "idio- pathic thrombocytopenic purpura one must be sure that the patient is not taking any medication which may be responsible for his disease This may require his admission to a hospital to isolate him from his usual environment The diagnosis can be established by testing the patient s response to the suspected drug after his platelet count has returned to normal A single small dose often suffices to reduce the platelet count perceptibly within a matter of hours In addition appropriate *in vitro* tests may dem onstrate platelet agglutination defective clot retraction comple

ment fixation and actual platelet lysis in the presence of the responsible agent (77)

The most important step in the treatment of thrombocytopenia due to sensitivity to a drug is to discontinue its administration Should there be alarming symptoms of bleeding treatment with corticosteroids in the same way that one treats acute idiopathic thrombocytopenic purpura may tide the patient over until his platelets rise to a normal level The prognosis is excellent barring hemorrhagic accidents prior to remission

THROMBOCYTOPENIA ASSOCIATED WITH INFECTIOUS DISEASES

A decrease in the concentration of platelets in the circulating blood may accompany or follow many infectious diseases in some as a constant feature and in others as an occasional or rare complication The pathogenesis of the thrombocytopenia is unknown An appealing speculation is that the thrombocytopenia which appears during convalescence from infectious diseases may reflect a reaction between the infectious agent and antibodies developed against it Adequate studies to test this point are not available It is difficult even to venture a guess concerning the origin of thrombocytopenia occurring at the peak of an infectious disease

Thrombocytopenia regularly accompanies epidemic hemorrhagic fever and cytomegalic inclusion disease two infectious diseases of unknown etiology *Epidemic hemorrhagic fever* is an acute febrile illness which was prevalent in United Nations forces during the Korean war (41) Nearly every patient had a hemorrhagic tendency which began as early as the second day of symptoms reached its zenith at the end of the first week and then gradually subsided The occurrence of hemorrhagic phenomena was correlated with a decrease in the platelet count Megakaryocytes were present in normal or increased numbers in aspirated bone marrow (40 502) In addition to bleeding these patients also experienced hypotension and renal insufficiency Epidemic hemorrhagic fever carries with it a relatively high case fatality rate I am unfamiliar with evidence concerning the mechanism or treatment of thrombocytopenia in this disease

Cytomegalic inclusion disease is a fatal disorder usually of premature infants characterized by thrombocytopenic purpura

jaundice, enlargement of the liver and spleen, lethargy respiratory distress and anemia (427) The white blood cell count is ordinarily normal or elevated This disease is thought to be viral in origin for inclusion bearing cells are found in the kidney liver and lungs Again, the pathogenesis and treatment of the thrombocytopenia are unknown

In most other infectious diseases, thrombocytopenia is rare The list of infections complicated by a decrease in the platelet

TABLE VII

INFECTIONS WHICH MAY BE COMPLICATED BY THROMBOCYTOPENIA*

Viral or Probably Viral	Measles rubella chicken pox mumps epidemic hemorrhagic fever cytomegalic inclusion disease influenza small pox vaccinia cat scratch fever infectious hepatitis infectious mononucleosis
Rickettsial	Typhus
Bacterial	Pneumococcal pneumonia typhoid fever meningococcal meningitis or meningococcemia gonococcal infection erysipelas scarlet fever diphtheria, anthrax dysentery staphylococcemia proteus sepsis tuberculosis bacterial endocarditis pertussis brucellosis
Spirochetal	Syphilis relapsing fever
Protozoan	Malaria kala azar
Metazoan	Ankylostomiasis

* Adapted from (660) and (715) The evidence relating thrombocytopenia to these infections varies in the degree of conviction it carries

count is legion (660 Table VII) For example thrombocytopenia has been described in patients with the exanthemata mumps infectious mononucleosis diphtheria typhus typhoid fever acute infectious hepatitis tuberculosis subacute bacterial endocarditis and various respiratory infections, including pneumococcal pneumonia epidemic influenza and even the common cold Often the published evidence that these infections are causally related to the accompanying thrombocytopenia is sketchy In cases of thrombocytopenia subsequent to acute infection the diagnosis of acute idiopathic thrombocytopenic purpura is often made but this terminology is probably best avoided

The thrombocytopenia which occasionally accompanies severe influenza or typhoid fever appears at the height of the disease

and may contribute to the hemorrhagic nature of lethal cases (660 250) Thrombocytopenia also occurs early in the course of infectious mononucleosis leading to its confusion with acute leukemia megakaryocytes are found in normal or increased numbers in aspirated marrow Thrombocytopenic purpura may be the sole clinical manifestation of infectious mononucleosis the diagnosis becoming clear only upon laboratory study (254a)

Thrombocytopenia in tuberculosis is nearly always associated with the miliary form of the disease the spleen is usually palpable In other cases the patients seem to have primary tuberculosis of the spleen without miliary spread In either instance megakaryocytes are present in the marrow In one of our patients who had tuberculosis in the lungs and spleen splenectomy was followed by a prompt remission of the bleeding tendency and the platelet count rose to normal However if hemorrhagic symptoms are not alarming it is probably wiser to treat the tuberculosis prior to surgery In any event the treatment of thrombocytopenia accompanying tuberculosis should not include the use of corticosteroids unless antibiotics are administered concomitantly

The thrombocytopenia associated with measles (285) rubella (5) mumps (332) or chickenpox (707) is noted in the first month and usually the first two weeks after the onset of the illness In measles the fall in the platelet count may begin during the height of the rash (485) but purpura is uncommon before the period of convalescence In rubella too the rash may be succeeded within a few days by purpura (203a) In patients with thrombocytopenia complicating these infections the bone marrow is ordinarily normal in appearance (5 707) although there may be no signs of platelet formation at the margins of the megakaryocytes The thrombocytopenia may be of great severity and there may be alarming and even fatal bleeding More usually however the thrombocytopenia associated with the exanthemata is benign and recovery takes place within a few weeks or months Since the patients or their families are often fearful that the diagnosis is leukemia the physician should reassure them of the probable nature of the illness Ordinarily if a history of recent infection has been obtained and there is no evidence suggesting a more malignant process examination of the bone marrow may be deferred

jaundice enlargement of the liver and spleen lethargy, respiratory distress and anemia (427) The white blood cell count is ordinarily normal or elevated This disease is thought to be viral in origin, for inclusion bearing cells are found in the kidney liver and lungs Again the pathogenesis and treatment of the thrombocytopenia are unknown

In most other infectious diseases thrombocytopenia is rare The list of infections complicated by a decrease in the platelet

TABLE VII

INFECTIONS WHICH MAY BE COMPLICATED BY THROMBOCYTOPENIA*

Viral or Probably Viral	Measles rubella chicken pox, mumps epidemic hemorrhagic fever cytomegalic inclusion disease influenza small pox vaccinia cat scratch fever infectious hepatitis infectious mononucleosis
Rickettsial	Typhus
Bacterial	Pneumococcal pneumonia typhoid fever meningococcal meningitis or meningococcemia gonococcal infection erysipelas scarlet fever diphtheria anthrax dysentery staphylococcemia proteus sepsis tuberculosis bacterial endocarditis pertussis brucellosis
Spirochetal	Syphilis relapsing fever
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including seven of nine with eclampsia Three of the eight thrombocytopenic patients had gross hemoglobinemia and hemoglobinuria during the eclamptic episode Indeed evidences of hemolysis were present in seventeen of twenty seven cases of toxemia of pregnancy (507 508) The pathogenesis of acute hemolytic anemia and thrombocytopenia in this syndrome is obscure The similarity between the renal lesions of eclampsia and lupus erythematosus suggests a common mechanism but the L E test has been consistently negative in toxemia of pregnancy One wonders whether an auto immune reaction may be fundamental to the pathogenesis of toxemia of pregnancy

Rarely a combination of thrombocytopenia hemolytic anemia and renal failure somewhat reminiscent of toxemia of pregnancy may appear in infants and young children The erythrocytes may be severely distorted The fundamental nature of this syndrome is disputed its relationship to thrombotic thrombocytopenia has been suggested Although death may occur from renal failure the disorder is self limited (730 731)

THROMBOCYTOPENIA IN SYSTEMIC LUPUS ERYTHEMATOSUS

The frequency with which systemic lupus erythematosus is accompanied by thrombocytopenia has provided further support for the view that a decrease in the number of circulating platelets may be a manifestation of hypersensitivity Thrombocytopenia occurs in a fourth to a half of cases of systemic lupus erythematosus (433 273) Sometimes a syndrome indistinguishable from idiopathic thrombocytopenic purpura may be the first manifestation of the disease (314 326) Only after the passage of months or even years does the true diagnosis of systemic lupus erythematosus emerge (671) In other cases cutaneous lesions of lupus may be present but other manifestations of this disease may be long delayed In still others thrombocytopenia is detected only after the appearance of obvious symptoms of lupus

The etiology of the thrombocytopenia observed in systemic lupus erythematosus is unknown The marrow contains numerous megakaryocytes and cannot be distinguished from that of idiopathic thrombocytopenic purpura (117) Although it is entertaining to consider the role of antigen antibody reactions this view is still unproved Intriguingly Nathan and Snapper (456) ob

for a week or two until it is clear that the thrombocytopenia is persistent The therapy of thrombocytopenia associated with the exanthemata is not different from that of patients with acute idiopathic thrombocytopenic purpura with which it is often confused

THROMBOCYTOPENIA ASSOCIATED WITH HEMOLYTIC ANEMIA

Additional information concerning the possible role of immune mechanisms in the pathogenesis of thrombocytopenia has been obtained from studies of patients with *acute hemolytic anemia* Evans (195) found that thrombocytopenia was common in cases of acute idiopathic hemolytic anemia Conversely, the direct Coombs test was positive in six of eleven patients whom he thought had idiopathic thrombocytopenic purpura Evans interpreted these data to indicate that thrombocytopenia in acute hemolytic anemia might be due to an auto immune reaction Indeed he demonstrated that the serum of one patient with acute hemolytic anemia and thrombocytopenia agglutinated normal platelets Similarly Tullis (669) observed platelet lysins in the serum of two of seven patients with acute hemolytic anemia and thrombocytopenia Thrombocytopenia is also a common concomitant of severe reactions to the transfusion of incompatible blood These observations seem to support the concept that antigen antibody reactions may result in thrombocytopenia However the possibility must be entertained that some other mechanism is responsible for the fall in the platelet count accompanying hemolysis Conceivably the lysed red blood cells introduce phospholipids into the circulation which induce intravascular coagulation This mechanism has been offered to explain the thrombotic complications of paroxysmal nocturnal hemoglobinuria (398) and may account for the thrombocytopenia observed in a fifth or more of patients with this disease (135 398)

The treatment of acute hemolytic anemia is not altered by the presence of thrombocytopenia Corticosteroids and splenectomy are the usual measures employed often without striking benefit

Two special varieties of hemolytic anemia and thrombocytopenia are worthy of mention In toxemia of pregnancy death often results from hemorrhage particularly into the brain Among twenty eight patients thrombocytopenia was detected in eight

cases appear between the ages of twenty and fifty Females are affected more often than males The onset of symptoms is often dramatic Weakness headache neurologic changes abdominal pain and evidences of a bleeding tendency are common within the first day or two of the illness Occasionally urticaria (39), Raynaud s phenomenon (230) or generalized enlargement of the lymph nodes (650) may precede other symptoms by some weeks The patient may present a striking picture of confusion disorien tation hallucination or schizoid behavior Aphasia or other speech disturbances may appear with suddenness Paresis or paralysis focal paresthesia or anesthesia clonic or choreiform movements ocular palsies cortical blindness generalized convulsive seizures and coma may appear Papilledema may be present Sometimes such signs of meningeal irritation as nuchal rigidity and a positive Kernig s may be elicited The neurologic signs change rapidly waxing and waning for no obvious reason (468)

The bleeding tendency resembles that of any severe throm bocytopenic purpura The anemia is often manifested by extreme pallor and mild icterus Fever often of considerable intensity is almost invariable The patient sometimes complains of myalgia or arthralgia The skin may have a cafe au lait hue Moderate en largement of the liver or spleen may be found and less frequently generalized enlargement of lymph nodes Cardiac arrhythmias have been observed

The results of laboratory studies are relatively uniform A pro found normocytic normochromic anemia is commonly noted at the first examination The hemolytic nature of the anemia recog nized by Moschcowitz (447) is supported by the presence of reticulocytosis hyperplasia of the erythroid elements in the mar row slight elevation of the indirect reacting bilirubin in serum urobilinogenuria and nucleated red blood cells in peripheral blood Rarely hemoglobinemia may be detected There may be spherocytosis and increased fragility of red cells to hypotonic solutions (451) but the Coombs test and test for agglutinins and hemolysins are usually negative and mechanical fragility is not increased (600) The white blood cell count is often moderately elevated with neutrophilic leukocytosis frequently accompanied by the presence of many immature forms

served that the platelet count was depressed in the newborn infant of a woman with thrombocytopenia and lupus as if the responsible agent had crossed the placenta Further observations of this nature would be of the greatest interest

In patients with thrombocytopenia associated with systemic lupus erythematosus treatment with corticosteroids may result in a transient rise in the platelet count (612) Remission follows splenectomy in a high percentage of cases, although relapse may then occur (524a) Study of the spleen will often demonstrate the periarterial fibrosis characteristic of lupus, even when other evidences of the disease are not yet patent (273) Whether indefinite treatment with corticosteroids or splenectomy is the treatment of choice is not yet clear Dameshek (145 143 524a) has wondered whether splenectomy may not accelerate the appearance of other lesions of lupus but this view is by no means universal

Although thrombocytopenia is the commonest cause of purpura in patients with systemic lupus erythematosus this symptom may reflect other abnormalities In different cases, purpura may be related to the presence of a circulating anticoagulant directed against the middle stages of clotting (page 110) or to hyperglobulinemia (page 205) macroglobulinemia (page 207) or cryoglobulinemia (page 211) The possibility that purpura may be due to a vascular defect (471 118) or to concomitant azotemia must also be considered

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura first described by Moschcowitz (447) in 1925 is an acute usually fatal disorder involving many organ systems characterized by fever, hemolytic anemia, thrombocytopenia and neurologic changes The syndrome is disguised in the literature under the usual battery of names, including thrombotic microangiopathy thrombocytopenic vertical angionecrosis or platelet thrombosis syndrome (43, 599 37, 372)

The clinical picture pathologic changes and prognosis are remarkably uniform Although thrombotic thrombocytopenic purpura has been recognized in a ten months old baby (712), most

the central nervous system present Abdominal pain a common symptom has been attributed to such diverse lesions as fat necroses within the pancreas bleeding into the ovary and perforation of hemorrhagic intestinal ulcers Although the thrombocytopenia was originally explained by inclusion of the platelets within the vascular lesions it is possible that the production of platelets is suppressed The morphologic appearance of the megakaryocytes does not help to differentiate these two possibilities No explanation for the fever or hemolytic anemia is available

The diagnosis of thrombotic thrombocytopenic purpura is suggested by the tetrad of fever thrombocytopenia hemolytic anemia and neurologic changes Occasionally the diagnosis has been confirmed prior to death by finding characteristic lesions in the bone marrow liver muscle skin appendix or spleen However examination of these tissues is seldom helpful during life and the thrombocytopenia limits the procedures which may be feasible

The etiology of thrombotic thrombocytopenic purpura is unknown Although the fulminant febrile course is similar to that of an infectious process no microbial agent has been identified Soumerai and MacGillivary have pointed out similarities between this disease and the Shwartzman phenomenon (622) A more popular view compares the lesions to those of hypersensitive reactions Thus thrombotic thrombocytopenic purpura might be grouped with such diffuse disorders as systemic lupus erythematosus and polyarteritis nodosum It is of interest that cutaneous lesions resembling those of systemic (230) or discoid (426 536) lupus erythematosus are observed in a few cases About a fifth of patients have a history of rheumatic fever or arthritis In other patients the disease has begun shortly after the administration of sulfonamides penicillin or other possible antigens and many of these patients have had hypersensitive reactions to these agents Although a sharp distinction is usually drawn between thrombotic thrombocytopenic purpura and lupus the possibility exists that the two are different manifestations of the same fundamental process The histologic changes in the glomeruli are similar and periarterial fibrosis and verrucous endocarditis lesions characteristic of lupus have been seen in thrombotic thrombocy

Profound thrombocytopenia and its concomitants have been observed in nearly every case Megakaryocytes (665) are found in normal numbers in aspirated marrow but usually their cyto plasm does not appear to be producing platelets The cerebro-spinal fluid is often under slightly increased pressure, and may contain increased amounts of protein and twenty to forty white blood cells per cu mm

The course of thrombotic thrombocytopenic purpura is usually stormy and swift Many patients die within a week of the onset of symptoms and only about half live more than a month Even the most transient remissions are exceptional The disorder is al most invariably fatal although a few patients have survived for several years The cause of death is often obscure Sometimes damage to the central nervous system seems responsible In other instances renal failure or myocardial damage may contribute But often no specific reason can be found other than the severe nature of the patient s illness

Pathologically the most arresting feature of thrombotic throm bocytopenic purpura is the presence of characteristic amorphous and granular occlusions within the lumen of arterioles and capil laries throughout the body These are probably composed of plugs of fibrin (130) Platelets, once thought to be the core of these plugs cannot be demonstrated by differential staining techniques (211 648) The occlusions are associated with proliferation of the vascular endothelium (470) The walls of the arterioles are in filtrated with homogeneous acidophilic fibrinoid material Unlike other diffuse vascular disorders little or no inflammatory reaction surrounds the affected vessels (39) Orbison (470) was impressed by the frequency of aneurysmal dilatation of the damaged walls of the smallest blood vessels particularly at the arterio capillary junction Since vascular changes may be seen in the absence of intravascular occlusions Orbison believes that the initial lesion is in the vascular wall

The neurologic abnormalities of patients with thrombotic thrombocytopenic purpura may be explained by focal areas of necrosis which result from widespread thrombotic vascular lesions located particularly in the grey matter of the cerebral hemis pheres and brain stem (468) Only rarely is gross bleeding into

topenic purpura has come from studies using a variety of approaches but whether the low platelet count is due to impaired formation or excessively rapid destruction of platelets or both is not yet answered The megakaryocytes although present in normal or increased numbers in aspirated specimens of bone marrow do not show the platelet like bodies normally found at the periphery of their cytoplasm and their appearance has been interpreted as immature or quiescent Within a day after splenectomy the megakaryocytes of a patient with idiopathic thrombocytopenic purpura are surrounded by large numbers of platelets and become more normal in appearance Such observations have been interpreted in two ways The rapid restoration of the normal morphologic appearance of the megakaryocytes and the rise in the platelet count have suggested to some that the formation or release of platelets is depressed in some patients with idiopathic thrombocytopenic purpura The removal of the spleen removes this depression and thus corrects the thrombocytopenia (144 368 558) Extracts of the spleen have been prepared which produce thrombocytopenia in animals (666) but difficulty has been experienced in repeating these experiments A contrary opinion suggests that the megakaryocytes are not so much depressed as exhausted In this view, the megakaryocytes of a patient with idiopathic thrombocytopenic purpura are working at full speed to produce platelets which are being destroyed at an excessive rate elsewhere in the body splenectomy is beneficial because the spleen may remove from the circulation platelets which have been damaged by a thrombocytopenia producing agent (267) Of course these two possibilities that the spleen inhibits the release of platelets and that it removes platelets from the circulation are not mutually incompatible

There seems little doubt that the life span of the platelet is greatly shortened in patients with idiopathic thrombocytopenic purpura For example Hirsch and Gardner (286) and Stefanini and Dameshek (632) observed that normal platelets transfused into such patients disappeared from the circulation more rapidly than normally Presumably then the survival of platelets is impaired in idiopathic thrombocytopenic purpura

No single hypothesis can explain adequately the pathogenesis

topenic purpura It is of interest that close relatives of patients with thrombotic thrombocytopenic purpura have been said to have idiopathic thrombocytopenic purpura, systemic lupus erythematosus polyarteritis nodosum and the fulminant variety of eclampsia characterized by evidences of hemolytic anemia and thrombocytopenic purpura The association of malignant thymoma and thrombotic thrombocytopenic purpura in one case is noteworthy in view of the coincidence of benign thymic tumors and aplastic anemia (page 130)

By and large therapy has been ineffective Splenectomy has often been performed but only rarely has this procedure been followed by remission of symptoms (228 426) Usually ACTH and corticosteroids fail to arrest the progress of the disease al though Burke and Hartmann (100) observed improvement after the use of large doses

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura or Werlhof's disease is a term encompassing those instances of thrombocytopenia in which the low platelet count cannot be attributed to some other disorder Characteristically, the spleen is not palpable, the mar row contains adequate numbers of megakaryocytes and the pa tient s symptoms are limited to manifestations of a bleeding tendency The designation idiopathic thrombocytopenic purpura undoubtedly encompasses more than one disease Two groups of patients can be discerned those with an acute self limited dis order in which death or recovery usually occurs within three or four months and those with a chronic protracted disease lasting for many years Idiopathic thrombocytopenic purpura occurs at all ages though acute self limited cases are more frequent during the first two decades of life It is hopeless to attempt to delineate the disease from the published literature since most writers in clude cases in which thrombocytopenia may have been caused by infection or sensitivity to drugs or may have been a manifestation of a systemic disorder such as systemic lupus erythematosus It is reasonable to guess that further subdivision of the syndrome of idiopathic thrombocytopenic purpura will occur

An appreciation of the pathogenesis of idiopathic thrombocy

of cases of idiopathic thrombocytopenic purpura (263) Agglutinins are more likely to be found in individuals with chronic rather than acute thrombocytopenic purpura (632) However the significance of these platelet agglutinins and lysins is confused by a lack of correlation among the results of tests performed by different methods and positive tests have been reported in patients with thrombocytopenia secondary to splenomegaly or with acute hemolytic anemia without thrombocytopenia (669 425)

The hypothesis that idiopathic thrombocytopenic purpura may be associated with a circulating antibody like agent leaves unexplained the role of the spleen Histologic examination of the extirpated spleen does not reveal any pathognomonic changes in this disease (281 517) Since the thrombocytopenia producing agent may persist in the blood stream after splenectomy (266) it is probable that the spleen does not play a fundamental part in the pathogenesis of idiopathic thrombocytopenic purpura More likely platelets, damaged by the circulating agent are removed by the spleen by mechanisms which are not necessarily abnormal

None of these observations answers the fundamental question as to the etiology of idiopathic thrombocytopenic purpura Evidence has already been presented that thrombocytopenia may accompany any disorder in which an antigen antibody reaction may participate in the pathogenesis of symptoms The view that idiopathic thrombocytopenic purpura is the result of an autoimmune reaction is attractive but still unproved Finally one must reiterate that cases formerly classified as examples of idiopathic thrombocytopenic purpura are now recognized to be instances of such diverse disorder of systemic lupus erythematosus acute hemolytic anemia or sensitivity to drugs

Acute Idiopathic Thrombocytopenic Purpura Many of the cases reported as instances of acute idiopathic thrombocytopenic purpura accompany or follow an infection (400 462) These are probably not true examples of idiopathic thrombocytopenic purpura *yet in any given case it is difficult to establish a causal re*lationship between the infection and the low platelet count Although pediatricians speak of acute thrombocytopenic purpura subsequent to the acute respiratory infections of children there is scarcely a time that children can be said to have been free of

of these changes in platelet formation and survival In the last few years interest has centered upon the possibility that the plasma of patients with idiopathic thrombocytopenic purpura contains an agent which depresses the number of circulating platelets The existence of this agent—often called an antibody—receives support from at least three types of observation The newborn infants of women with idiopathic thrombocytopenic purpura may have transient thrombocytopenia during the first weeks of life, as if an agent producing thrombocytopenia crosses the placenta to the child (page 158)

A second form of evidence for the concept of a circulating thrombocytopenia producing agent has been furnished by the remarkable experiments initially performed by Harrington and his associates (266) Plasma obtained from patients with idiopathic thrombocytopenic purpura was transfused into normal individuals Within thirty to sixty minutes the recipients platelet counts began to fall reached a minimum within two to three hours and did not return to normal for four or more days Sometimes the thrombocytopenia was of great severity and petechiae, ecchymoses and other evidences of a bleeding tendency appeared The rapid fall in the number of circulating platelets suggested that they were destroyed by a process initiated by the transfused plasma However, the recipient s megakaryocytes also showed changes resembling those of idiopathic thrombocytopenic purpura, their cytoplasm no longer containing budding platelets The question remains unanswered whether the thrombocytopenia producing agent acts both upon the megakaryoctes and upon the circulating platelets Because of the difficulties inherent in human experimentation, relatively little is known about the properties of the thrombocytopenia producing agent other than that it is associated with a relatively heat resistant globulin of serum (266)

Finally a mass of confusing data suggests that the serum of some patients with idiopathic thrombocytopenic purpura alters normal platelets *in vitro* Evans (195) Stefanini (629) Dausset (148), Harrington (267) and others have demonstrated that such serum agglutinates platelets and under certain conditions may induce their lysis Positive tests have been found in half or more

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such infections for very long However, Newton and Zuelzer (462) noted that in children acute thrombocytopenic purpura was relatively more frequent during the winter and spring as if the disorder resulted from infection or its treatment In other cases, acute thrombocytopenic purpura occurs as a sequel to the ingestion of some drug or exposure to some other allergen to which the patient is sensitive If appropriate studies demonstrate this relationship, such cases should not be considered instances of acute idiopathic thrombocytopenic purpura

After excluding all these cases instances of acute thrombocytopenia still remain in which the pathogenesis is essentially unknown In these idiopathic cases, the clinical course is remarkably similar to that of cases which can be attributed to infection or sensitization Acute thrombocytopenic purpura occurs with about equal frequency in males and females and although it may affect individuals of any age it is probably more frequent in children than in adults Usually the onset is sudden and the patient is aware when the purpuric symptoms appear Bleeding follows the usual pattern associated with thrombocytopenia Hirsch and Dameshek (285) were impressed that petechiae and ecchymoses most often appear first upon the legs or about the mouth or at the site of a pre existing rash The spleen is usually not palpable Laboratory studies demonstrate not only the decrease in circulating platelets but often an increase in the bleeding time a positive tourniquet test and poor prothrombin "consumption Examination of the marrow shows normal or increased numbers of megakaryocytes which may fail to show budding of platelets at the periphery

Ordinarily recovery occurs spontaneously within weeks or at most two or three months after the onset of the illness unless the patient has died of hemorrhage A lethal outcome is usually due to bleeding into the central nervous system

The prognosis of acute idiopathic thrombocytopenic purpura cannot be defined accurately from published data Some authors (335) describe case fatality rates as high as 20 per cent yet our own experience has been much more favorable only one death has occurred during the last nine years at University Hospitals of Cleveland The risk of fatal hemorrhage is probably greatest dur

ing the first month of the disease (335 697) The outlook is said to be particularly poor in idiopathic thrombocytopenic purpura which first appears during pregnancy (715)

Chronic Idiopathic Thrombocytopenic Purpura The diagnosis of chronic idiopathic thrombocytopenic purpura may well be reserved for patients in whom the disease has been present for six months or longer since spontaneous remissions are rare after this time In contrast to acute idiopathic thrombocytopenic purpura the chronic disorder usually becomes manifest more gradually and the patient does not consult the physician until some months have passed One patient whom I studied had had purpura for twenty two years before the diagnosis of idiopathic thrombocytopenic purpura was suggested Indeed if the patient brings his disease to the attention of the physician early in its course the *diagnosis often does not become clear until the passage of some* months Chronic idiopathic thrombocytopenic purpura occurs at any age but in two-thirds of the cases its onset is before the age of twenty (285) In contrast to the acute disease females are more likely to be affected than males the ratio varying in different series from 3 1 to 3 2 Despite repeated descriptions of the familial nature of chronic idiopathic thrombocytopenic purpura this disorder is probably not hereditary confusion with other diseases and hear say evidence may account for some of these reports

The symptoms of chronic idiopathic thrombocytopenic purpura are the same as those of the acute disorder except for the less striking onset In the female menorrhagia is often a prominent feature (146) and many of our female patients have been referred by gynecologists Chronic bleeding into the adnexal region may lead to abdominal pain and distress and may contribute to the difficulties some of these patients have in initiating and maintaining pregnancy At times the first indication of a bleeding tendency may be hemorrhage subsequent to dental extraction or some other minor surgical procedure In one series one eighth of cases were found accidentally (285)

Physical examination in patients with chronic idiopathic thrombocytopenic purpura reveals only the evidences of a bleeding tendency Although Hirsch and Dameshek (285) described a palpable spleen in one fifth of their cases in my own experience

this is unusual In cases in which the tip of the spleen can be felt the patient usually has some other disorder such as miliary tuberculosis or systemic lupus erythematosus (190) Lymph nodal enlargement has also been described but again this sign ordinarily reflects some other disorder *Rarely, superficial ulceration* of the skin of the legs may be present, this usually heals subsequent to splenectomy (285 717)

Laboratory findings are similar to those of acute thrombocytopenic purpura Examination of the bone marrow is essential to exclude other causes of protracted thrombocytopenia If hemorrhage has been severe erythroid hyperplasia may be present The principle diagnostic difficulty concerns the differentiation between chronic idiopathic thrombocytopenic purpura and systemic lupus erythematosus Often the diagnosis of lupus will become clear only after the lapse of many years although careful examination of the spleen after its removal may reveal periarterial fibrosis long before other manifestations of the disease are present The L E test may or may not be positive in cases ultimately diagnosed as lupus this test should be performed in all patients with chronic idiopathic thrombocytopenic purpura

The course of chronic idiopathic thrombocytopenic purpura is protracted and the likelihood of spontaneous remission is slight The patients seem to have periods of increased bleeding followed by remissions but these cycles do not correlate well with objective platelet counts In females the exacerbations may coincide with the menstrual periods (440, 483)

The *treatment of idiopathic thrombocytopenic purpura* is now being debated with vigor In the acute illness—that is in patients in whom symptoms have been present for less than six months—therapy should usually be conservative The danger of bleeding into the central nervous system is maximal during the first week or two of the disease after which the chances of lethal hemorrhage are greatly diminished The treatment of choice in acute idiopathic thrombocytopenic purpura is probably the administration of corticosteroids for three or four weeks—for example 15 mg of prednisone every eight hours—after which the dose is gradually decreased Nearly always this therapy will increase the platelet count suppress symptoms or both Larger doses may be

needed to produce the desired response (715) If symptoms recur when therapy is discontinued it may be reinstituted In many cases however, relapse does not occur presumably, the steroids merely tide the patient over until recovery occurs in the natural course of events If steroid therapy is without effect either on the platelet count or on symptoms it should be discontinued after several weeks Unless alarming bleeding occurs it is probably wiser to delay splenectomy until a minimum of six months after the onset of symptoms since spontaneous remission is most likely to occur within this period

If severe bleeding occurs during the course of acute idiopathic thrombocytopenic purpura the question of splenectomy will be raised This procedure carries with it a heavier risk during an acute episode than during a quiescent period but occasionally the severity of symptoms may justify the procedure The result of splenectomy for acute idiopathic thrombocytopenic purpura are difficult to interpret because of the natural tendency of this syndrome to remit Moreover in contrast to chronic cases improvement may be delayed for a week or more after splenectomy suggesting that the operation is not causally related to the remission Another therapeutic measure likely to be considered when bleeding is severe is the transfusion of platelet rich blood or of concentrates of platelets but this procedure provides only the most temporary benefit (630 392)

The management of cases of chronic idiopathic thrombocytopenic purpura is more sharply disputed Once the disease has lasted for six months spontaneous remissions are exceptional Until steroid therapy was available splenectomy first suggested by Kaznelson in 1916 was the usually accepted treatment This operation is followed by remission in two thirds of cases but the platelet count does not rise in the remainder (697 524 355 558) However in some patients in whom the platelet count does not increase bleeding may nonetheless diminish subsequent to the procedure Often after splenectomy the bleeding time decreases and the tourniquet test changes toward normal prior to an increase in peripheral platelet count (388 537) Perhaps the first effect of the operation is directly upon the blood vessel wall or the first platelets which become available for hemostasis are con

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The course of chronic idiopathic thrombocytopenic purpura is protracted and the likelihood of spontaneous remission is slight The patients seem to have periods of increased bleeding followed by remissions but these cycles do not correlate well with objective platelet counts In females the exacerbations may coincide with the menstrual periods (440 483)

The *treatment of idiopathic thrombocytopenic purpura* is now being debated with vigor In the acute illness—that is in patients in whom symptoms have been present for less than six months—therapy should usually be conservative The danger of bleeding into the central nervous system is maximal during the first week or two of the disease after which the chances of lethal hemorrhage are greatly diminished The treatment of choice in acute idiopathic thrombocytopenic purpura is probably the administration of corticosteroids for three or four weeks—for example 15 mg of prednisone every eight hours—after which the dose is gradually decreased Nearly always this therapy will increase the platelet count suppress symptoms or both Larger doses may be

A contrary view has been expressed by Watson Williams (697) and by Carpenter (107a) Watson Williams and his associates observed that in chronic idiopathic thrombocytopenic purpura remission subsequent to treatment with corticosteroids was not sustained for more than sixty days whether or not therapy was continued during this period They therefore believe that sple nectomy should be performed during the first weeks of treatment regardless of the platelet count About two thirds of their pa tients responded to splenectomy perhaps some of these may ultimately suffer a relapse for in patients studied four years or longer only half had normal platelet counts Carpenter s (107a) experience is similar

A conservative program for the management of patients with chronic idiopathic thrombocytopenic purpura can be deduced from these various observations The patient should be admitted to the hospital to minimize the chance that the disorder is due to sensitization to a drug or to some other antigen If thromboc ytopenia persists after a week or two splenectomy should be per formed with the expectation that remission will occur in about two thirds of patients Occasionally when the patient fails to respond to splenectomy the platelet count can be maintained by therapy with corticosteroids More often patients who have not had a remission after splenectomy do not respond to steroid therapy No treatment is available for these patients except to tide them over a crisis when the platelet count may be raised for a few hours by the repeated transfusion of platelet rich plasma obtained preferably from a patient with polycythemia vera and collected with plastic equipment (227 630) Another method of treating an acute exacerbation of bleeding is the administration of massive doses of corticosteroids for a brief period as advocated by Weisberger and Surhland (705) Neither platelet transfusions nor massive corticosteroid therapy is entirely satisfactory Trans fused platelets disappear from the patient s circulation rapidly Large doses of corticosteroids may not be tolerated well and severe and even fatal complications of this therapy may ensue

When splenectomy for chronic idiopathic thrombocytopenic purpura is not followed by remission or the disease relapses the possibility that accessory spleens were overlooked at operation is

sumed in the process Only when a reserve supply becomes avail able does the peripheral blood count rise In patients who will respond, the cytoplasm of the megakaryocytes may show changes suggesting the formation of platelets (144) within the first day after splenectomy The peripheral platelet count rises, and may reach normal levels as soon as twenty four to forty eight hours after surgery The platelet count may then continue to rise so that the patient may have supra normal platelet counts for weeks and even years after splenectomy In chronic idiopathic throm bocytopenic purpura, if the platelet count does not rise above the lowest normal levels within a week it is unlikely that it will later reach higher values Indeed it is my experience that the count subsequently falls again to sub normal levels

With the advent of steroid therapy it was found that these hormones induce a temporary remission in about half of cases and reduce the bleeding tendency in others (557, 61, 517) The use of corticosteroids thus may provide protection against bleed ing until the diagnosis of idiopathic thrombocytopenic purpura seems clear and its chronic nature is established The permanence of the remission induced by corticosteroids in true chronic idio pathic thrombocytopenic purpura is disputed Dameshek (147) treated some nineteen patients with chronic idiopathic throm bocytopenic purpura with an initial dose of 20 to 100 mg of prednisone per day After an average of about fifteen days of treatment normal platelet counts were achieved in twelve pa tients and almost normal counts in two others The dosage of prednisone was then gradually decreased Four of these patients were weaned entirely away from drug therapy without relapse In others maintanence dosage was required a procedure which was accompanied by hyperadrenocorticism and in at least one case osteoporosis Dameshek formerly an advocate of splenec tomy now reserves this operation for patients with severe throm bocytopenic purpura who do not respond to therapy with ster oids He (143 524a) fears that splenectomy will induce an exacerbation of systemic lupus erythematosus a complication which appeared in some 25 per cent of his cases of supposed idiopathic thrombocytopenic purpura He points out that this adverse effect of splenectomy cannot be predicted in advance

or even bleeding into the central nervous system Bleeding tends to be more severe in infants whose mothers have overt purpura at the time of delivery (559) During the first day or two of life the platelet count is often very low It is during this period that the infant may die of bleeding The platelet count gradually increases but two or three months may elapse before the normal level is reached Fortunately symptoms usually last no longer than the first two or three days of life

Although the exact cause of the thrombocytopenia is not known a reasonable assumption is that it results from the transmission of a circulating agent from the maternal to the infant s plasma (670 193) Indeed Vandenbrouck and Verstraete (674) believes that they have demonstrated antibody like activity directed against platelets in the serum of infants with this disorder The disappearance of the thrombocytopenia after two or three months suggests that it takes this time for the circulating factor to be metabolized

Ordinarily no therapy is indicated other than protection of the infant from injury If severe or alarming bleeding is present transfusion of platelet rich blood or the administration of corticosteroids is indicated Some infants have been treated with splenectomy but this procedure seems unwarranted for a disease which is self limited particularly since it is still not entirely certain that splenectomy does not increase the susceptibility of infants to infection (237 609 329)

Reference has already been made to a similar disorder in the newborn infant of a patient with systemic lupus erythematosus complicated by thrombocytopenia (456) The infant s platelet count rose spontaneously to normal levels in about three weeks Lysins directed against platelets and a positive L E test were demonstrable in the infant s serum during the first few days of life As in the case of idiopathic thrombocytopenic purpura abnormal maternal proteins had evidently been transferred across the placenta to the infant

Mention has also been made of thrombocytopenia in the newborn infant whose mother has been given a drug to which she is sensitive For example if a sensitized mother is given quinine during the course of a delivery the newborn infant may have

certain to be suggested (133) At the time of splenectomy the surgeon should search carefully for accessory spleens and each of these should be removed However, cases in which relapses are due to the presence of accessory splenic tissue are exceptional (196) and usually reoperation is best avoided

Idiopathic Thrombocytopenic Purpura and Pregnancy Much has been made of the possibility that idiopathic thrombocytopenic purpura is graver in the pregnant than the non pregnant patient (715) However, in all probability, the maternal mortality rate is not significantly different than in non pregnant patients (490) Idiopathic thrombocytopenic purpura in pregnant patients must be differentiated from thrombocytopenia due to sensitivity to drugs of which quinine and quinidine are probably those most frequently at fault Thrombocytopenia also complicates the hypo fibrinogenemic accidents of pregnancy and severe toxemia of pregnancy The therapy of idiopathic thrombocytopenic purpura during pregnancy differs in only one respect from that of non pregnant patients There is some reason to believe that the use of steroids during the first trimester of pregnancy may be deleterious for the fetus (264) so that hormone therapy should be avoided during this period

THROMBOCYTOPENIA IN THE NEWBORN INFANT

Additional support for the relationship between thrombocy topenia and antigen antibody reactions comes from studies of thrombocytopenia in the newborn infant An abnormally low platelet count in the first weeks of life may be due to one of several causes Needless to say studies of the pathogenesis of thrombocytopenia at this age are particularly difficult because of the problem of obtaining adequate specimens

Thrombocytopenia is observed in about half of the newborn infants of mothers who have idiopathic thrombocytopenic pur pura or have had a remission subsequent to splenectomy (193) On the other hand it does not appear in the newborn infant whose mother has had a spontaneous remission Purpuric symp toms are present at birth or appear within a few hours (559) Ordinarily only a few petechiae are noted Less commonly the infant is severely affected having ecchymoses mucosal bleeding

an inhibiting action upon the megakaryocytes there is evidence that the life span of the platelets is decreased (286) For this reason it seems more likely that the diseased spleen removes platelets from the circulation at an excessive rate or alters the platelets so that they are removed from the circulation pre maturely

Often the thrombocytopenia in patients with splenomegaly is sufficiently mild that no treatment is indicated In other cases purpura may be troublesome justifying therapy Except in pa tients with leukemia splenectomy is the treatment of choice and is followed almost uniformly by remission

THROMBOCYTOPENIA WITH SEQUESTRATION

In infants with *congenital hemangiomata* the number of plate lets in the circulating blood may be reduced far below normal levels (706) The pathogenesis of the thrombocytopenia in this condition has been studied by Good and his associates (239) who noted that the vessels of the tumor may be filled with platelet thrombi The inference that the thrombocytopenia is due to sequestration of the platelets within the vessels of the tumor is attractive Supporting this hypothesis blood expressed from the tumors may have a higher platelet count than peripheral blood (232) The marrow usually shows increased numbers of mega karyocytes which are not surrounded by budding platelets per haps because these cells cannot keep up with the demand (239) Splenectomy is not helpful but obliteration of the vascular lesion by x ray or excision is followed by remission In general the prognosis is excellent although relapse occurs if there is recur rence of the lesion

Perhaps similar in pathogenesis is the thrombocytopenia occa sionally observed in adults with *Kaposi s sarcoma* In one patient whom I studied the thrombocytopenia did not respond to therapy with corticosteroids

One entertaining speculation attributes the thrombocytopenia associated with splenomegaly to the increased size of the splenic sinusoidal bed which offers a large area for sequestration of the platelets Transient thrombocytopenia apparently due to seques

transient thrombocytopenia No therapy is indicated since the offending agent will be rapidly eliminated from the infants blood

In other cases transient thrombocytopenic purpura, clinically similar to that of the newborn infants of thrombocytopenic mothers may occur even though the maternal history is entirely negative Harrington (267) has suggested that in such instances the mother may have acquired isosensitivity to the infants platelets In this view maternal antibodies directed against the infants platelets cross the placental barrier to produce thrombocytopenia, a pathogenesis analogous to that of erythroblastosis fetalis The thrombocytopenia is self limited and ordinarily no therapy is indicated Direct evidence for the existence of this syndrome has been reported recently (228a)

Thrombocytopenic purpura is also a rare complication of erythroblastosis fetalis The pathogenesis of the fall in the platelet count is unclear Although such infants may die of bleeding more usually the thrombocytopenia only contributes to the patients other difficulties

Familial thrombocytopenia of the newborn infant with congenital anomalies is described in Chapter XIII

THROMBOCYTOPENIA IN PATIENTS WITH SPLENOMEGALY

Purpura accompanied by a low platelet count is found in many conditions related to each other only by the presence of enlargement of the spleen For example thrombocytopenia is common in *congestive splenomegaly with or without cirrhosis* of the liver (56 540) Gauchers disease (154) sarcoidosis (205) lympathic leukemia tuberculosis or brucellosis (89a) involving the spleen Hodgkins disease (173) and Feltys syndrome of rheumatoid arthritis splenomegaly and leucopenia (297) In most of these disorders megakaryocytes are present in aspirated bone marrow in normal or increased numbers these cells may or may not show evidences of platelet formation at their periphery Little is known about the pathogenesis of the thrombocytopenia in these cases *Occasionally the serum* contains agglutinins or lysins against platelets Although many authors believe that the spleen exerts

Chapter XV

THROMBOCYTOPENIA IN WHICH THE PATHOGENESIS IS UNKNOWN

Congenital thrombocytopenia with eczema and repeated in fections Aldrich Steinberg and Campbell (20) described a family in which thrombocytopenic purpura was associated with repeated ear infections eczematoid dermatitis and bloody diarrhea The disorder appeared in some but not all males in this family and seemed to be transmitted from generation to generation as a sex linked recessive trait In one child thrombocytopenia persisted despite splenectomy although the marrow contained numerous megakaryocytes these cells showed little evidence of platelet formation

A number of similar cases have been described all in male infants (295 338 719 438) Evidences of purpura are present at birth or become manifest shortly thereafter These children suffer from repeated infections such as furunculosis otitis media pneumonia peritonitis or meningitis Various offending bacterial agents have been isolated The white blood cell count and the concentration of gamma globulin in the serum are normal (438) Several of the patients have had eosinophilia leading Huntley and Deeds (295) to suggest that the eczema may have an allergic basis The syndrome is invariably fatal within a few months or years after birth either from infection or from the results of bleeding despite the usual therapeutic procedures Splenectomy has been performed repeatedly with only the most transient of benefit and the administration of corticosteroids has been equally useless Histologically the spleen has been unremarkable except for the presence of non specific splenitis The nature of this disease then and its treatment are entirely unknown

tration of platelets, is also seen in *experimental hypothermia* (13) The platelets return to the peripheral circulation when the animal is rewarmed

SELECTED REFERENCES

43 Barondess J A Thrombotic thrombocytopenic purpura Review of the literature and report of 3 cases *Am J Med 13* 294 1952

193 Epstein R D Lozner E L Cobbey T S and Davidson C S *Congenital thrombocytopenic purpura Am J Med 9* 44 1950

239 Good T A Carnazzo S F and Good R A Thrombocytopenia and giant hemangioma in infants *A M A J Dis Child 90* 260 1955

263 Harrington W J Therapy of the purpuras *J Chronic Dis 6* 365 1957

264 Harrington W J *The Purpuras* Disease a month Chicago Year Book Publishers 1957

285 Hirsch E O and Dameshek, W "Idiopathic" thrombocytopenia Review of 89 cases with particular reference to differentiation and treatment of acute (self limited) and chronic types *A M A Arch Int Med 88* 701 1951

426 Meacham G C Orbison J L Heinle R W Steele H J and Schaefer J A Thrombotic thrombocytopenic purpura A disseminated disease of arterioles *Blood 6* 706 1951

462 Newton W A Jr and Zuelzer W W Idiopathic thrombocytopenic purpura in childhood *New Eng J M 245* 879 1951

Chapter XVI

THROMBOCYTHEMIA

ONE of the most puzzling hemorrhagic syndromes is the bleeding tendency accompanying the presence of greatly increased numbers of platelets in peripheral blood Despite considerable recent work, no satisfactory explanation of this paradox is available

Thrombocytosis any state in which the number of platelets in the circulating blood is increased is relatively common The platelet count frequently increases slightly several days after injury surgical procedures or parturition A persistent, moderate increase in the platelet count is also common after splenectomy in otherwise normal individuals This mild thrombocytosis is probably without significance although some believe that it causes an increased tendency to thrombosis

A platelet count more than twice the normal value—above 600 000 per cubic millimeter by the direct method—is rarer and of much greater interest (403) This "thrombocythemia" is frequently a feature of polycythemia vera and chronic myeloid leukemia It also occurs in association with myeloid metaplasia of any cause (303) particularly in patients in whom splenectomy has been performed (536) or in whom the spleen has atrophied Thrombocythemia has been noted after the removal of an infarcted spleen and after splenectomy in cirrhosis of the liver or splenic vein thrombosis or during the surgery of carcinoma of the stomach. Indeed it is said that thrombocythemia may follow splenic atrophy *or splenectomy regardless of the underlying dis*ease Thrombocythemia has also been described in a variety of other disorders including bronchial carcinoma with metastases to the marrow hyperadrenalism sarcoidosis tuberculosis and perhaps Paget s disease of bone

Familial thrombocytopenia unassociated with anemia (page 129) or with repeated infections must be very rare (517 285) Wooley (721) described a family in which a man his son and one of two daughters had thrombocytopenia The marrow contained large numbers of quiescent megakaryocytes Splenectomy, performed for bleeding in one case, was followed by remission

Onyalai is a strange disorder, endemic in East, Central and South Africa in which hemorrhagic bullae appear on the surface of the mucous membranes particularly of the mouth It is confined almost exclusively to natives in whom it is said to occur most frequently during periods of famine Onyalai occurs in two forms, an acute fulminant type which is rapidly fatal and a more chronic variety in which the symptoms may last for months or years Death may result from exsanguination from the nose urinary tract gastrointestinal tract or uterus The hemorrhagic state is uniformally associated with severe thrombocytopenia

The etiology and pathogenesis of onyalai are obscure Merskey (430) has suggested that thrombocytopenia is due to the ingestion of some toxic agent Patients with untreated onyalai are said to excrete excessive amounts of ascorbic acid in their urine it is claimed that they may respond to the administration of large amounts of this vitamin (645) An earlier vogue for treatment by the intramuscular injection of the patient s own blood has apparently passed

Kwashiorkor a nutritional disturbance of weanling infants is occasionally complicated by purpura sometimes associated with thrombocytopenia (431) The mechanisms inducing the fall in the platelet count are not known

Heat stroke (715 722a) and *thermal burns* (715) are said to cause thrombocytopenia The mechanisms responsible are unknown

SELECTED REFERENCES

20 Aldrich R A Steinberg A G and Campbell, D C Pedigree demonstrating a sex linked recessive condition characterized by draining ears eczematoid dermatitis and bloody diarrhea *Pediatrics* *13* 133 1954

722a Wright D O Peppert L B and Cuttino J T Purpuric manifestations of heat stroke Studies of prothrombin and platelets in 12 cases *A M.A Arch Int Med* *77* 27 1946

remain in the circulation increasing the platelet count I am unfamilar with evidence supporting these speculations

How the increase in the platelet concentration causes a bleed ing tendency is only partially understood The bleeding time is often greatly prolonged but the results of this test are erratic In one patient for example the bleeding time was two or three minutes on some occasions and greater than fifteen minutes at other times In the test tube platelet function is usually normal if one dilutes the platelets to the concentration present in normal plasma On the other hand even normal platelets inhibit "throm boplastin generation" if they are concentrated to the numbers found in patients with thrombocythemia (298) Possibly the in hibitory properties of concentrated platelets are important in the origin of the bleeding tendency The serotonin concentration of platelets is low in thrombocythemia but the evidence that this substance is needed for hemostasis is equivocal

Other laboratory tests reflect the condition responsible for the thrombocytosis For example the red cell count may be elevated in polycythemia vera or after splenectomy for cirrhosis or throm bosis of the portal vein On the other hand in myeloid metaplasia the patient is anemic In one of my patients bleeding due to thrombocythemia produced an anemia which temporarily ob- scured the diagnosis of polycythemia vera The white blood cell count is elevated in some patients with polycythemia in patients with myeloid leukemia or myeloid metaplasia and in many pa tients who have had splenectomy for various reasons The pro thrombin time clotting time and prothrombin consumption test are normal Clot retraction is normal if correction is made for the hematocrit in patients with polycythemia the red cell mass may obscure the fact that the degree of retraction is normal The tourniquet test is usually normal (615)

The most successful treatment of thrombocythemia in my hands has been the administration of radioactive phosphorus a tech nique advised by many authors (216 720) Unfortunately this method cannot be applied to patients with myeloid metaplasia who can ill afford further depression of their blood forming tis sues Its use is limited to patients with polycythemia vera or myeloid leukemia those in whom splenectomy has been per

A group of patients remains in whom no obvious cause for extreme thrombocytosis is present (715) Although this syndrome has been called primary thrombocytosis or thrombocythemia it is likely that some of these cases are instances of polycythemia vera or myeloid leukemia Gunz (254b) and Ozer and his associates (476a) point out that the spleen is usually enlarged in patients with primary disease

About three fourths of patients in whom the direct platelet count is 600 000 per cubic millimeter or higher have evidences of a hemorrhagic tendency, bleeding most commonly from the mucous membranes (615) Epistaxes gingival bleeding and bleeding from the gastrointestinal tract are the most usual symptoms The patients may also bleed after dental extractions minor lacerations and, rarely from the urinary tract or even into the central nervous system Hemorrhage following surgery has been described Cutaneous purpura is distinctly rare

Patients with thrombocythemia are said to have a tendency to thrombosis Thromboses are probably more common among those patients who have polycythemia vera or myeloid leukemia, but this complication has been described in other situations for example after removal of an infarcted spleen Among other possible manifestations of intravascular thrombosis priapism has been described repeatedly

The platelet count has been reported to be as high as 14 000 000 per cubic millimeter by methods in which the normal count averages 250 000 The mechanism responsible for the elevation in the platelet count is unclear and probably differs from case to case Whether increased platelet production decreased destruction (33a) or both cause the thrombocytosis is not certain Except in cases of myeloid metaplasia the number of megakaryocytes in the marrow is increased In one of my patients megakaryocytes were numerous in a lymph node removed at biopsy In this patient splenectomy had been performed for portal hypertension secondary to cirrhosis of the liver In one study the life span of the circulating platelets was normal (358) If excessive production is at fault, perhaps the spleen fails in its role in destroying or removing platelets On the other hand when the spleen has atrophied or been removed it is possible that superannuated platelets

Chapter XVII

FAMILIAL DISORDERS CHARACTERIZED BY A LONG BLEEDING TIME

THE familial hemorrhagic diseases in which an abnormally long bleeding time is associated with a normal concentration of platelets are most perplexing (194 553 617 90 291 613) The confusion is reflected in the nomenclature terms such as pseudohemophilia von Willebrand s disease Glanzmann s disease thrombopathy and thrombasthenia being used indiscriminately The newly introduced methods of study of the hemorrhagic disorders have permitted the division of these cases into several groups These several syndromes are strikingly similar clinically, but can usually be distinguished with reasonable ease by laboratory methods The nomenclature which I shall use is arbitrary and capricious and the reader must remember that other authors may use different terms The term *thrombocytopathic purpura* will be applied to cases in which bleeding is associated with qualitative abnormalities of the circulating platelets Two principal types have been described one in which clot retraction is impaired and a second in which thromboplastic activity develops poorly in shed blood In *vascular hemophilia* the abnormally long bleeding time is accompanied by a deficiency of antihemophilic factor The term *pseudohemophilia* will be used to describe cases in which the bleeding time is prolonged but no other abnormalities are consistently demonstrated in the laboratory by currently available techniques The latter group of cases has been diminished by the delineation of vascular hemophilia and its further subdivision seems likely as new means of study are devised

THROMBOCYTOPATHIC PURPURA

That qualitative abnormalities in platelets might be causally related to abnormal bleeding was first proposed by Glanzmann

formed for some irrelevant reason and those with "primary" thrombocythemia

The prognosis is that of the underlying disease I studied a patient who had thrombocytosis for at least six years prior to her demise and this is by no means an unusual course

SELECTED REFERENCES

198 Fanger H Cella L J Jr and Lichtman H Thrombocythemia Report of 3 cases and review of literature *New Eng J Med* 250 456 1954

261 Hardisty R M and Wolff H H Haemorrhagic Thrombocythaemia *Brit J Haemat* 1 390 1955

303 Jackson D P Hartmann R C and Conley C L Clot retraction as a measure of platelet function II Clinical disorders associated with qualitative platelet defects (Thrombocytopathic purpura) *Bull Johns Hopkins Hosp* 93 370 1953

403 Mallarmé J and Auzepy P Distinction nosographique (clinique et hématologique) des thrombocythémies *Le Sang* 28 210 1957

morphologically abnormal (303) Such observations suggest that the expression of the defect may vary from individual to individual.

In addition to impaired clot retraction these patients often have abnormally long bleeding times although in any one case the results of this test may change from time to time The tourniquet test may be positive The platelet count is nearly always normal In one patient moderate thrombocytopenia was corrected by splenectomy but the bleeding tendency and the impairment of clot retraction were unaffected by the procedure (303) In ordinary stained preparations the appearance of the platelets has varied in different cases In some instances no gross abnormalities can be seen while in others the platelets seem bizarre and irregular in shape and contain coarse granules Often the agglutination of platelets so commonly seen in normal blood smears is absent (165) The megakaryocytes in stained smears of aspirated bone marrow appear normal

More specialized techniques substantiate the pathologic nature of the platelets The pseudopods normally seen at the periphery of the platelets by electron microscopy are absent and the platelets do not spread out in a normal manner (90) The platelets may have increased resistance to lysis by hypotonic solutions (457)

Functional studies also demonstrate the abnormal character of the platelets in this type of thrombocytopathic purpura When the coagulation of plasma is observed by phase microscopy the forming fibrin strands do not orient to the platelets as they would normally (303) Moreover the addition of such abnormal platelets does not induce clot retraction in normal platelet-deficient plasma or in blood obtained from patients with thrombocytopenia (165)

The functional abnormality of the platelets does not extend to their role in blood clotting The thromboplastin generation and prothrombin consumption tests are not impaired in thrombocytopathic purpura with impaired clot retraction and platelets obtained from patients with this disease correct the abnormal prothrombin "consumption" of thrombocytopenic blood (165)

The prognosis in thrombocytopathic purpura with impaired clot retraction must be guarded because blood loss from epistaxis

(234) In his patients a bleeding tendency was accompanied by morphologic changes in platelets and defective clot retraction a syndrome he called hereditary hemorrhagic thrombasthenia Some of his patients had thrombocytopenia as well Since Glanzmann s studies, bleeding has frequently been attributed to abnormalities of platelet function Unfortunately in most of the reported cases the techniques used to establish these abnormalities do not withstand critical examination (99) There are however, occasional patients in whom a bleeding tendency is associated with evidence that the function of the platelets is impaired Two groups of cases have been delineated those in which clot retraction is defective and those in which the clot promoting properties of the platelets are deficient Although these two types may exist separately both abnormalities may be present simultaneously In addition bleeding has been occasionally attributed to other defects in the function of the platelets

Authentic cases of *thrombocytopathic purpura with impaired clot retraction* are undoubtedly rare In one series of 1 062 cases of hemorrhagic disease only three instances were discovered (156) My own experience encompasses only two cases The disorder is life long bleeding may follow circumcision in the neonatal period (165) Typically, the patient bruises more readily than normally He may have spontaneous ecchymoses Excessive bleeding may follow dental extractions tonsillectomy and other surgical procedures Epistaxes are common and may be so profuse as to threaten life Bleeding from the gums and gastrointestinal tract is common but hematuria is said to be unusual Menstrual bleeding may be exceptionally profuse one of our patients required repeated transfusions to combat blood loss Our second patient did not have menorrhagia but on one occasion had severe blood loss from the ovary apparently initiated by ovulation Hemarthroses hematomas and bleeding into the central nervous system are fortunately rare

In a number of patients with thrombocytopathic purpura with impaired clot retraction other members of the family have had a bleeding tendency However no typical pattern of inheritance has been established In one interesting case the patient s father and sister had no significant symptoms yet their platelets were

greatly prolonged but the platelet count is either normal or only slightly depressed In smears of peripheral blood the platelets may be grossly abnormal in appearance and giant forms resembling lymphocytes are common (90) The chromomere may be massed at the center of the platelets as a very dense body simulating a nucleus The platelets do not form the clusters usually found in the normal blood smear They may be more resistant than normal to lysis by hypotonic solutions (457) Although the megakaryocytes in the bone marrow do not look unusual when stained in the conventional way special techniques may bring out qualitative abnormalities (486)

The abnormal function of the platelets is reflected in impaired prothrombin "consumption" when whole blood is allowed to clot The abnormality is localized to the platelets for prothrombin "consumption" is normal when the patient s plasma is mixed with normal platelets and abnormal when the patient s platelets are mixed with normal plasma (58) In the thromboplastin generation test the patient s platelets function poorly as if their "cephalin" like properties were deficient or unavailable for clotting (619) Tests for other coagulative abnormalities are unremarkable The concentration of antihemophilic factor is within normal limits distinguishing this disease from vascular hemophilia The tourniquet test may be positive

As in the case of thrombocytopathic purpura with impaired clot retraction experience is too limited to assess prognosis but instances of fatal bleeding are relatively common The transfusion of fresh citrated blood may provide transient hemostasis again the possibility that the corticosteroids may provide temporary benefit should be tested

In addition to the hereditary thrombocytopathic purpuras a case described by Alexander (32) suggests the possibility that a similar defect may occur as an acquired disorder Qualitative abnormalities in the platelets have also been described in azotemia (Chapter XXVI) and in osteogenesis imperfecta (Chapter XVIII)

VASCULAR HEMOPHILIA

Vascular hemophilia is a hereditary hemorrhagic disease of both sexes in which the bleeding time is prolonged and the con

or menorrhagia may be profuse Experience in authenticated cases is too limited to know whether the disease is life threatening under conditions in which the lost blood can be replaced Other forms of therapy are unsatisfactory The use of local pressure and such hemostatic agents as bovine thrombin may help to stop hemorrhage in accessible areas The transfusion of fresh citrated blood containing normal platelets may be helpful deVries (165) observed temporary correction of the bleeding tendency and normal clot retraction after a transfusion of just 600 ml It is not clear whether the newer corticosteroids such as prednisone will improve hemostasis, their use should be tested under carefully controlled conditions

From the theoretic point of view, thrombocytopathic purpura with impaired clot retraction is of the greatest importance The relationship between clot retraction and hemostasis has been disputed, one authority asserts that retraction is only an atavistic remnant of the function of platelets in non mammalian species (99) The co existence of bleeding and impaired clot retraction in these patients indicates that clot retraction has a more fundamental role in human hemostasis

In a second type of thrombocytopathic purpura the platelets behave adequately with respect to clot retraction but fail to function in a normal manner during blood clotting The clinical picture in *thrombocytopathic purpura with impaired blood clotting* does not differ significantly from that of patients with thrombocytopathic purpura with impaired clot retraction The life long tendency to bleed excessively is manifest in the same way again hemarthroses hematomas and bleeding into the central nervous system are unusual Thrombocytopathic purpura with impaired blood coagulation is familial but the method of inheritance seems different in different cases In families described by Braunsteiner (90) and Bernard and his associates (59) the defect appeared to result from the inheritance of non sex linked recessive genes Supporting this view several cases have arisen from consanguineous marriages On the other hand in Jackson s family (303) the defect seemed to be transmitted as a dominant trait

The diagnosis of thrombocytopathic purpura with impaired blood clotting is based upon the demonstration of characteristic abnormalities in laboratory tests The bleeding time is usually

suggested by Schulman and his associates (577) seems more appropriate. In affected individuals the titer of antihemophilic factor has ranged from less than 1 per cent to as much as 75 per cent of normal (465). On the average the concentration of antihemophilic factor is higher than in most cases of classic hemophilia. In the same family the concentration of antihemophilic factor may be abnormal in some affected individuals and normal in others. The variability in the deficiency of antihemophilic factor among reported cases is reflected in a variability in serum prothrombic activity; this test is abnormal only when the deficiency of antihemophilic factor is severe.

These studies of vascular hemophilia led to re-examination of the Aland Island bleeders (322, 464) and the discovery that their titer of antihemophilic factor was often moderately low. Thus von Willebrand's pseudohemophilia and vascular hemophilia are evidently the same disease. This redefinition of von Willebrand's pseudohemophilia leaves certain fundamental questions unanswered. No satisfactory explanation exists for the deficiency of antihemophilic factor. If the deficiency is genetically determined, does this mean that the synthesis of this protein is influenced by several genes? Or is antihemophilic factor utilized at an excessive rate in patients with vascular hemophilia? Even more disturbing is the prolonged bleeding time. Since this test is normal in severe classic hemophilia, a deficiency of antihemophilic factor alone cannot explain the abnormal bleeding time in vascular hemophilia. On the other hand, the evidence that the blood vessels themselves are defective (388) is conflicting (627). Perhaps, as Matter suggested (224), a single gene is needed both for a step in the synthesis of antihemophilic factor and for the development of the vascular tree. On the other hand, Nillson (465) wonders whether in vascular hemophilia the plasma is not only deficient in antihemophilic factor but in addition lacks something needed to prevent bleeding from small blood vessels. This explanation, like Matter's, suggests the co-existence of two distinct defects.

In large measure, the prognosis of vascular hemophilia varies with the severity of the deficiency in antihemophilic factor. Individual episodes of bleeding should be treated as if the patient had classic hemophilia. Most authors believe that the transfusion

centration of antihemophilic factor in the plasma is abnormally low The delineation of this syndrome has had a curious history For many years von Willebrand, Jurgens and their associates (682, 321) made exhaustive studies of a bleeding disorder preva lant among inhabitants of the Aland Islands in the Baltic sea to which the name pseudohemophilia was given The disease occurs in both sexes and is familial, it seems to be inherited as a dominant trait Its severity varies considerably from case to case even within the same family, so that bleeding is trivial in one individual and lethal in another The symptoms do not differ significantly from those of classic hemophilia except that he marthroses are unusual and permanent joint deformities have not been reported (627) Since the bleeding tendency occurs in fe males menorrhagia and bleeding at parturition are prominent features of the disease In contrast to classic hemophilia cutane ous petechiae are sometimes observed (321)

Many similar cases have been described but their identity with the disorder observed in Aland Islanders has not always been clear For a long time the nature of the defect was disputed Laboratory tests demonstrate that the bleeding time is prolonged but the platelet count and clotting time are normal the tourniquet test is often positive Originally Jurgens and von Willebrand (321 683) thought that the platelets were qualitatively defective while Macfarlane (388) and others believed that the capillaries reacted abnormally to injury Recently new evidence has radical ly altered thinking concerning the pathogenesis of symptoms in these patients

In 1953 Alexander and Goldstein (27) and Larrieu and Soulier (348) described several patients with a bleeding tendency in whom dual defects were detected As in von Willebrand s cases the bleeding time was prolonged despite the presence of normal numbers of platelets In some instances the capillaries in the nail beds were irregular and distorted In addition the plasma of these patients was deficient in antihemophilic factor Since their reports many similar cases have been described (601 627) The clinical manifestations of this new" syndrome are indistinguishable from those of the Aland Islanders leading Singer and Ramot (601) to use the name pseudohemophilia type B" Vascular hemophilia"

prolonged bleeding time The tourniquet test is positive in perhaps half of cases To satisfy the diagnostic criteria for pseudohemophilia the platelet count should be normal the platelets should be normal morphologically and platelet function as measured by clot retraction prothrombin "consumption" and "thromboplastin generation" should be normal The plasma should contain normal amounts of the recognized clotting factors

The fundamental nature of the pathologic process in pseudohemophilia is not clear but the clinical and laboratory manifestations are consistent with a lesion within the smallest blood vessels themselves Examination of the capillary loops at the bed of the fingernails by direct microscopy may reveal morphologic abnormalities and impaired contractility after injury (388) However similar changes have been described in vascular hemophilia

Indeed whether pseudohemophilia and vascular hemophilia are separate diseases is not yet clear Certainly the symptoms of the two disorders are indistinguishable In vascular hemophilia the essential feature is the moderate decrease in the concentration of antihemophilic factor but the titer of this substance may be normal in some affected relatives of patients with this disease (224) For this reason one cannot be sure that a bleeder thought to have pseudohemophilia does not in fact have vascular hemophilia This confused state of affairs will continue until a sufficient number of families have been studied to establish satisfactory criteria for the differentiation of pseudohemophilia and vascular hemophilia The prognosis in pseudohemophilia is usually excellent although the patients may be plagued by their bleeding symptoms Menorrhagia may be so intractable that hysterectomy is performed but it would probably be preferable to induce artificial menopause Bleeding in an accessible area may be controlled by pressure and the use of such hemostatic agents as topical thrombin or Russell's viper venom If blood loss is severe the patient may require blood transfusion However one of our patients died of intractable bleeding from the gastrointestinal tract after more than 100 transfusions had been given If the administration of fresh blood seems to correct the bleeding tendency one should suspect that the true diagnosis is vascular hemophilia rather than pseudohemophilia

The foregoing discussion has emphasized my uncertainty

of fresh blood or freshly frozen plasma corrects both the defect measured *in vitro*, and the bleeding tendency (577) The transfusion of purified antihemophilic factor (71) or the administration of cortisone (614) are said to be ineffective

PSEUDOHEMOPHILIA

The term pseudohemophilia has been used to describe many different hemorrhagic states I shall reserve it to define a life long disease in which a prolonged bleeding time is the only consistent abnormality detected with currently available tests Recent developments in methodology have so changed our views concerning patients in whom the bleeding time is long that, looking backward, it is difficult to classify the many published cases No one who has studied patients with pseudohemophilia is satisfied that each year will not bring new methods of subdividing this syndrome

Pseudohemophilia occurs in both sexes The bleeding tendency usually appears early in life indeed bleeding from the umbilical cord has been described (291) Patients bleed profusely from minor injuries and after surgical procedures, dental extractions and parturition Menorrhagia may be severe Gingival bleeding epistaxes and bleeding from the gastrointestinal tract are common There may be bleeding from other sites but if hemarthroses occur the diagnosis of pseudohemophilia should be questioned Spontaneous or post traumatic ecchymoses are frequent but petechiae are unusual An important feature of pseudohemophilia is the unpredictable nature of the bleeding on one occasion injury or surgery is followed by protracted bleeding and on another hemostasis seems normal

Pseudohemophilia is familial and is inherited as a dominant trait (386) However not everyone who carries the trait is affected clinically In one family studied at University Hospitals of Cleveland the disease has appeared in a man, his daughter and her son The severity of the clinical manifestations and of the abnormality in the bleeding time differs from individual to individual within a family Indeed in any one patient the bleeding time varies from time to time

In the present state of knowledge the diagnosis of pseudohemophilia is made only by the exclusion of other causes of a

Chapter XVIII

HEREDITARY DISEASES OF CONNECTIVE TISSUE

OCCASIONALLY bleeding is a prominent and troublesome feature of three of the hereditary disorders of connective tissue the Ehler Danlos syndrome osteogenesis imperfecta and pseudoxanthoma elasticum as if blood vessels lacked adequate extravascular support in these conditions

The diverse manifestations of the *Ehler Danlos syndrome* include hyperelasticity of the skin hyperextensibility of the joints a blue cast to the sclerae dislocation of the lens of the eye diaphragmatic hernia dissecting aneurysm of the aorta and splenomegaly (399) The India rubber men of the side shows are afflicted with this disease Ready bruising and subcutaneous hematomas are frequent leading to the formation of subcutaneous pseudo tumors Other manifestations include cutaneous petechiae epistaxes gingival bleeding melena hematuria hemoptyses and menorrhagia Hemorrhage into the muscles may be particularly troublesome There may be excessive bleeding from wounds after childbirth or after dental extraction tonsillectomy or other surgical procedures (391)

The cause of Ehler Danlos syndrome is unknown It is a hereditary disorder of both sexes which seems to be inherited as a simple dominant trait but its manifestations may not appear until early adult life The basic nature of the lesion is disputed McKusick (399) believes that the Ehler Danlos syndrome is a disorder of collagen but Rothman (570) and Tunbridge (672) have emphasized that the dermis contains an increased number of elastic fibers to which they attribute the excessive elasticity of the skin An extensive study of the hemostatic mechanisms in this disorder has demonstrated only that the tourniquet test may be

whether pseudohemophilia, in the sense that I have defined it, is a true entity As new techniques for the analysis of hemorrhagic disease are evolved, patients in whom this diagnosis has been made must be continually re evaluated Still, there is no reason to believe that a bleeding tendency may not be due to an intrinsic disorder of small blood vessels Some support of this view comes from the careful study of a patient in whom a severe bleeding tendency appeared in his 60th year (84) In this patient who had carcinoma of the stomach the only abnormal finding was a prolonged bleeding time This case, then, appeared to be an acquired form of pseudohemophilia

SELECTED REFERENCES

90 Braunsteiner H and Pakesch F Thrombocytasthenia and thrombocytopathia—old names and new diseases *Blood 11* 965 1956

191 Estren S Medal L S and Dameshek W Pseudohemophilia, *Blood 1* 504 1946

291 Horler A R and Witts L J Hereditary capillary purpura (von Willebrand s Disease) *Q J Med ns 27* 173 1958

303 Jackson D P Hartmann R C and Conley C L Clot retraction as a measure of platelet function II Clinical disorders associated with qualitative platelet defects (Thrombocytopathic purpura) *Bull Johns Hopkins Hosp 93* 370 1953

464 Nilsson I M Blomback, M Jorpes E Blomback B and Johannson S A V Willebrand s disease and its correction with human plasma fraction 1 0 *Acta Med Scand 159* 179 1957

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positive and the number of platelets may be moderately diminished (545a) Needless to say no therapy is available

Osteogenesis imperfecta—brittle bones and blue sclerae—is not ordinarily thought of as a hemorrhagic disorder However, subcutaneous bleeding is an occasional symptom and may be the most prominent feature of the disease (264) Epistaxes, melena, hematomas and subconjunctival and preretinal hemorrhages have been described (229) Follis (213) has shown that the skin in osteogenesis imperfecta lacks normal adult collagen Bleeding might be supposed to occur because the blood vessels are poorly supported However, qualitative abnormalities of the platelets have been described (229, 598) This observation if confirmed suggests that the defect in hemostasis may be similar to that of thrombocytopathic purpura

In *pseudoxanthoma elasticum,* firm, discrete waxy papules appear in patches in the folds of the skin (399 378) These papules are white creamy or yellow in color and vary in size from that of a pin head to that of a pea The neck, axillae breasts perineum, antecubital and cubital areas popliteal fossae and periumbilical regions may all be involved The skin surrounding the papules is thickened coarse and granular and the region may be lacking in hair Telangiectases may be noted at the edge of typical lesions and the skin may seem lax redundant and relatively inelastic Characteristic gray brown angioid streaks may be present in the retina

Evidences of pseudoxanthoma elasticum ordinarily appear in childhood or early adult life It is a familial disorder of both sexes In most cases the disease seems to be due to the inheritance of abnormal recessive genes but there are families in which it appears to be a dominant trait (556) Bleeding from virtually every organ has been described (588) the gastrointestinal tract the nose the uterus the vagina, the central nervous system, the retina, the urinary tract the joints and the skin Bleeding from the stomach may originate in superficial mucosal ulceration visible by gastroscopy (378) Subarachnoid and gastrointestinal hemorrhage are particularly dangerous and are the chief causes of death in this disease

The pathologic changes in the skin in pseudoxanthoma elas

ticum are not clearly defined Large aggregates of material stain ing like elastic tissue accumulate in the deeper and middle zones of the corium (399) Whether the disease is due to an abnormality of the elastic tissue or of collagen fibers has not yet been resolved (556) In the stomach the capillaries and veins of the mucosa and submucosa may be widely dilated and the elastic membranes of the small and medium sized arteries seem to have undergone degeneration (324) Similar vascular changes may be seen else where in the body and may well be responsible for the bleeding tendency

No therapy has been suggested for this unfortunate disorder Gastrectomy performed for severe gastrointestinal bleeding has not been uniformly successful

SELECTED REFERENCE

399 McKusick, V *Heritable Disorders of Connective Tissue* Second Edi tion St Louis C V Mosby Co 1960

Chapter XIX

HEREDITARY HEMORRHAGIC TELANGIECTASIA

HEREDITARY hemorrhagic telangiectasia is a familial disorder in which sporadic bleeding occurs from vascular lesions distributed throughout the body, particularly in the skin and mucous membranes The clinical features of the disease were vividly outlined at the turn of the century by Osler (472) who shares eponymic rights with Parkes Weber (698) and Rendu (552)

The lesions of hereditary hemorrhagic telangiectasia are not visible at birth but gradually become evident during the second to fifth decades of life Osler (473) described three types of cutaneous or mucosal lesions, macules, spiders and nodules Typically the lesions of hereditary hemorrhagic telangiectasia blanche upon pressure The macule the earliest lesion to appear, is a small red pin point lesion found on the skin of the face and arms and less often on the trunk or legs Macules are also common on the mucous membranes of the tongue or nose particularly in Kiesselbach s area The spider or telangiectasis has a central punctum and superficially resembles the vascular spider of cirrhosis of the liver it may not evolve for as long as a decade after other lesions are noticed The nodule is a red violaceous or purple lesion as big as 5 to 7 mm in diameter, and often raised as much as 2 to 3 mm above the surrounding skin The nodules are noted later than the spiders from whose centers they seem to develop

Careful examination may demonstrate that the lesions of hereditary hemorrhagic telangiectasia are present not only in the exposed areas of skin but on the scalp the palmar surfaces of the hands the finger tips under the nails on conjunctival surfaces, the roof of the mouth tongue and gingivae, and even the retina rectum and vagina Telangiectatic lesions may be demonstrable by endoscopy in the esophagus and stomach The lesions may be

found in the lung most often in the form of pulmonary arterio venous fistulas and in the spleen the liver (296) and the kidney

The primary manifestation of hereditary hemorrhagic telangiectasia is hemorrhage which occurs with unpredictable frequency and violence Epistaxes beginning in late childhood are usually the first symptom The nosebleed may start spontaneously or when the patient picks or blows his nose In females epistaxes may be especially frequent during menstruation The nosebleeds may be so severe that the patient is temporarily incapacitated Indeed the blood loss may be fatal The nosebleeds occur less frequently during adolescence only to return in adult life The patient may also bleed from gastrointestinal genitourinary cutaneous or cerebral (289) lesions Hemoptysis is not unusual and may even be fatal Hemoptysis is more likely to come from a telangiectasis in the bronchial mucosa than from pulmonary arteriovenous fistulas Rarely the spleen may be enlarged by lesions in the splenic artery or pulp (578) Patients with hereditary hemorrhagic telangiectasia may have severe acute or chronic anemia undoubtedly the result of blood loss giving the patients a pale and waxy complexion

The coincidence of pulmonary arteriovenous fistulas and cutaneous or mucosal vascular lesions was first noted by Rodes (560) Upon careful examination more than half of patients with pulmonary arteriovenous fistulas are found to have hereditary hemorrhagic telangiectasia Clubbing of the fingers and toes cyanosis and polycythemia in the absence of cardiac enlargement bring the diagnosis of pulmonary arteriovenous fistula to mind (448) but these signs need not be present (289) The patient may have dyspnea on exertion and weakness Dizziness numbness faintness diplopia and even convulsive episodes have been described but their relation to the pulmonary lesions is not clear Rupture of the fistula may cause massive hemoptysis or hemothorax

On physical examination of a patient with a pulmonary arteriovenous fistula a murmur and thrill may be found over the affected area The murmur is usually continuous but may be heard only during systole X Ray examination may show a circular discrete lesion in the lung fluoroscopy may demonstrate its pulsatile na

ture If the patient tries *to exhale through a closed glottis* the lesion decreases in size while if he tries to inspire against a closed glottis it increases in size A vascular shadow from the hilum to the pulmonary lesion is sometimes seen by fluoroscopy or tomography The vascular nature of the shadow may be demonstrated by angiocardiography

A variety of lesions, such as cirrhosis of the liver and vertebral anomalies have been described in patients with hereditary hemorrhagic telangiectasia I suspect that in many instances these additional lesions are coincidental

The familial nature of hereditary hemorrhagic telangiectasia has been studied carefully and repeatedly (613 75) Both sexes are affected with equal frequency The disease is inherited as a dominant trait, for individuals with only one affected parent have typical lesions Earlier writers believed that the disorder skipped" generations This view must be taken sceptically, since the diagnosis may not be possible until late in life There is a tendency *for the distribution of lesions to be hereditary a situation* most clearly seen in patients with pulmonary arteriovenous fistulas Perhaps this is an explanation for some cases of so called familial epistaxis hemoptysis or hematuria in which other lesions typical of hereditary hemorrhagic telangiectasia have not been found

Surprisingly few descriptions of the pathologic changes of hereditary hemorrhagic telangiectasia have been published Hanes (258), studying the cases at the Johns Hopkins Hospital, described the typical telangiectasis as a blood vessel formed of single layers of endothelium without muscular or elastic tissue in its walls He believed that the earliest lesion is a dilated capillary, red in color As the lesion increases in size, the venules becomes involved giving the cutaneous telangiectasis a violaceous or purple color Bean (47) pointed out that the thinning of the muscular coat leads to bulging or ballooning of the walls of the vessels by pressure within the arterioles Thus the essence of the lesion is a small aneurysm Bird and Jaques (76) were impressed by the preponderance of venous lesions The involved veins were dilated and pursued a tortuous course They emphasized the wide distribution of lesions throughout all the major organs In their well studied cases the venous channels in the liver and pancreas expanded into cavernous hemangiomas

In pulmonary arteriovenous fistula the arteries and veins may be joined by one or more large communications or by a tangle of more or less distended vessels (448) The sac of the fistula may be paper thin (289) In more than a third of cases the arteriovenous fistulas are multiple (289)

The abnormal vessels in hereditary hemorrhagic telangiectasia do not react to stimuli which would ordinarily affect normal capillaries Macfarlane (388) showed that if a lesion is pricked it bleeds indefinitely whereas unaffected blood vessels in the nail beds of the same individuals contract normally All tests of bleeding and clotting have been unremarkable An occasional individual is said to have a positive tourniquet test (602), but this test is occasionally positive in normal individuals

The diagnosis of hereditary hemorrhagic telangiectasia ordinarily presents no difficulties as long as it is kept in mind In patients who have repeated epistaxes or unexplained gastrointestinal hemorrhages or hemoptyses lesions should be sought assiduously

Patients with hereditary hemorrhagic telangiectasia may live a normal span of years but may die prematurely from bleeding from the stomach from the nose or from pulmonary arteriovenous fistulas However the patient may be chronically disabled by repeated epistaxes and chronic anemia The disorder worsens with age with the appearance of more lesions and more hemorrhagic episodes A particularly grave complication is cerebral abscess which may occur in patients with pulmonary arteriovenous fistula (289)

The treatment of cutaneous or mucosal bleeding is unsatisfactory Such expedients as the use of electro coagulation radium and X irradiation have been unsuccessful One of Osler s patients suggested that the nasal vessels might be occluded by local pressure and Hurst and Plummer (296) constructed a simple apparatus to achieve this A finger cot was tied snugly with fine thread to the end of a small catheter Then the finger cot lubricated with oil or vaseline was inserted well back into the nostril and inflated either by a rubber bulb or by placing the open end of the catheter in the mouth In this way the finger cot applied firm pressure to the interior of the nasal fossa After the bleeding had stopped the finger cot was gradually deflated I have no

personal experience with this ingenious method but it is said to work (208)

Pulmonary arteriovenous fistulas may be excised surgically Hodgson and his associates (289) recommended excision for patients with cyanosis and polycythemia, for those who have had hemoptyses and for patients whose lesions appear to be increasing in size Unfortunately, the pulmonary lesions may be multiple The treatment of bleeding from the gastrointestinal tract is most unsatisfactory In one patient whom I observed, gastrectomy not only failed to reveal a specific site of bleeding but was disastrous for the patient gradually oozed to death

Systemic therapy has been disappointing although a report by Koch (331) that the administration of estrogens may be helpful is of interest Harrison (268) suggested that estrogens may transform the columnar nasal epithelial cells into squamous cells and in this way form a mechanical barrier protecting the nose from injury

Hypochromic microcytic anemia, common in patients with hereditary hemorrhagic telangiectasia should be treated with iron in the conventional manner (633)

SELECTED REFERENCES

47 Bean W B *Vascular Spiders and Related Lesions of Skin* Springfield Charles C Thomas 1958

289 Hodgson C H Burchell H B Good C A and Claggett O T Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula Survey of a large family *New Eng J Med 261* 625 1959

Chapter XX

SCURVY

ONCE the commonest hemorrhagic disease scurvy has become so rare that its clinical features have grown unfamiliar to the practicing physician Indeed several modern texts devoted to hemorrhagic disease do not even mention scurvy as a cause of bleeding Nonetheless in an occasional patient the diagnosis of scurvy must be entertained

Scurvy is due to a dietary deficiency of Vitamin C but the pathogenesis of its symptoms is only vaguely understood Scurvy is limited to humans primates and guinea pigs These species are unable to synthesize ascorbic acid from its precursor 1 gulonolactone and are therefore dependent upon exogenous sources for this vitamin (101) Ascorbic acid is needed for the formation and maintenance of intercellular substances including collagen fibers and hyaluronic acid (718) Most of the symptoms in scorbutic individuals can be interpreted as a reflection of the impairment of structure and function of intercellular substances In this view capillary bleeding a major feature of scurvy is due to structural weakness either of the cement substance binding the endothelial cells together or of the collagen fibrils adjacent to the capillaries

Scurvy is seen at the two poles of life In infants especially those who have never been breast fed scurvy begins between the second and twelfth month particularly during the second half of the first year of life On the other hand except in extraordinary circumstances it is seen in adults only in middle aged and elderly individuals who live alone cooking their own meager meals or eating at restaurants It is much commoner in men than in women and is one of the widower s plights Studies in experimental subjects corroborate the early views that scurvy

appears only after prolonged deprivation of ascorbic acid For example in Crandens (131) classic studies on himself the first symptoms of scurvy did not appear until he had eaten a Vitamin C deficient diet for 132 days and similar latent periods have been observed by other investigators Indeed the difficulty of producing scurvy in volunteers makes it the more remarkable when one sees a case under our present cultural conditions Ralli and Sherry (525) suggested that infection, hyperthyroidism, trauma and diarrhea may predispose the individual to this dis order

SCURVY IN ADULTS

Our knowledge of the clinical picture of scurvy has been greatly enhanced by studies in volunteers As the disease occurs in nature, the picture is often muddied by the concomitance of other deficiency states In adults the onset of scurvy is often slow and insidious The patient feels tired, weak and depressed His lassitude may be accompanied by a feeling of irritability Although the appetite deteriorates, most patients continue to eat until their swollen, painful gums prevent mastication (677) Breathlessness palpitation and even cyanosis of the lips may suggest a diagnosis of cardiac disease rather than of avitaminosis Then after a variable period the patients bones joints and the muscles of his extremities begin to ache most often at night When he stands he tends to flex his legs at the knees After several weeks tiny perifollicular ecchymoses or petechial hemor rhages appear upon the legs especially on the calves the backs of the thighs and the buttocks Microscopic examination of these early skin lesions demonstrates congestion and proliferation of the blood vessels around the hair follicles followed by extravasa tion and hemorrhage (489) The perifollicular lesions may spread and coalesce with adjacent ecchymoses until the entire extremity is involved As the disease progresses ecchymoses appear spon taneously at other parts of the body such as the abdomen face and arms (134) They are particularly likely to occur around the joints and in the skin overlying hematomas Splinter hemorrhages may be seen under the nails the axis of the hemorrhage being parallel to the long axis of the nail

Striking among the characteristics of adult scurvy are gingival

lesions found only in individuals who have teeth Observations in experimental subjects suggest that pre existing gingivitis and para-odontal disease predispose to gingival difficulty (489) The first observed lesions are tiny hemorrhages at the tips of the interdental papillae which become edematous Later the gums become purple boggy swollen necrotic and infected The teeth may be buried within the swollen gums superficially suggesting the lesions of monocytic leukemia or the toxic effects of dilantin The teeth may loosen and fall out

Hemorrhages may appear in other areas Hemorrhage into a muscle is common producing a painful brawny induration tender to the touch The patient may also have joint pain effusion or even hemarthrosis although the subperiosteal hemorrhages common in infants are unusual There may be epistaxes microscopic or gross hematuria diarrhea and melena menorrhagia or metrorrhagia and pleural or pericardial effusions which may be bloody Bloody peritoneal effusions may be accompanied by symptoms simulating acute surgical disease of the abdomen so that exploratory laparotomies have been performed unwittingly

This description has emphasized the hemorrhagic manifestations of scurvy In addition patients with scurvy often have subcutaneous edema most evident in the pretibial region Wounds heal poorly and scars may dehiss Hyperkeratosis of hair follicles similar to that seen in deficiency of Vitamin A is common Anemia although not observed in experimental scurvy is frequent in the natural disease

Scurvy is highly lethal when unrecognized or because of cultural circumstances untreatable Death when it comes is often from secondary infection In other cases the actual cause of death is obscure The patient may become cyanotic and have a rapid weak pulse and Cheyne Stokes respiration He may go into shock and die suddenly Sometimes convulsions precede death

SCURVY IN INFANTS

In infants the clinical picture of scurvy differs somewhat from that in adults Cutaneous bleeding is less likely to be an early symptom although all the cutaneous manifestations seen in adults may be present More often the mother and physician are

impressed by great tenderness of the extremities and by the infant s refusal to move his limbs He lies on his back absolutely still, with his legs flexed, widely abducted and externally rotated *(66) He* screams when his legs are touched or he is lifted to change his diapers The tenderness and the child s indisposition to move his extremities result from subperiosteal hemorrhages, located *most often at the lower femur and the upper end of the* humerus In severe cases there is separation of the epiphysis from the shaft of the bone Superficially the child s symptoms suggest acute osteomyelitis or rheumatic fever a disorder unusual in such young babies As in adults other hemorrhagic lesions are frequent in infants though gingival bleeding and swelling are seen only after the teeth have erupted Epistaxis, bleeding into the bowel or urinary tract and into the central nervous system are not unusual in severe cases Retrobulbar hemorrhage resulting in proptosis is a frightening symptom Sudden death may occur prior to the administration of effective therapy *(214)*

THE DIAGNOSIS AND TREATMENT OF SCURVY

A careful dietary history may lead to the diagnosis of scurvy in the patient with purpuric manifestations One should recall how little Vitamin C is needed as a preventative 10 mg per day were sufficient in experimental subjects Nearly every mother provides a source of Vitamin C for her infant but an occasional parent obsessed by the germ theory of disease carefully boils the orange juice, destroying its antiscorbutic properties Routine tests for hemostatic function *are not helpful* The *clotting time* and bleeding time are within normal limits Only in experimental animals is there even a hint of coagulative abnormality (212a) *A priori* one would expect the tourniquet test to be positive since petechial lesions are found in dependent areas In fact the tourniquet test is often normal—that is few or no petechiae appear in a circumscribed part of the forearm after the blood pressure cuff is inflated for a standard period of time However this same stress brings out many petechiae often large in size, on the dorsum of the hand and wrist Thus a supposedly negative test *does not tell the whole story Still the significance* of the tourniquet test is difficult to assess since positive tests may

not revert to normal after appropriate antiscorbutic therapy Rarely mild thrombocytopenia may be present but this is usually not sufficient in itself to produce hemorrhagic symptoms (633) Qualitative abnormalities of the platelets have also been described

The diagnosis of scurvy may be fortified by determination of the concentration of Vitamin C in the buffy coat of peripheral blood (525) In experimental subjects symptoms do not appear until a month or more after detectable Vitamin C has disappeared from the buffy coat In the naturally occurring disease the buffy coat may contain traces of Vitamin C Thus the absence of Vitamin C from the buffy coat confirms but does not establish the diagnosis of clinical scurvy Examination of the plasma is not satisfactory for its content of Vitamin C may be below the measurable level without clinical evidence of scurvy

Scurvy is one of the few hemorrhagic diseases for which a satisfactory method of treatment is available Peters and his associates (489) demonstrated in experimental subjects that bleeding stopped within a week after the administration of as little as 10 mg of ascorbic acid a day Within seven to nine weeks only residual pigment was left in the skin Hemorrhage at the site of experimental wounds disappeared in about two months The gums healed more slowly and did not look normal for about three months In clinical practice much larger doses of ascorbic acid are used and healing is correspondingly faster For example Vilter (677) recommends that the average case of scurvy in adults be treated within 50 to 100 mg of ascorbic acid three to five times a day until 4 grams have been administered In critically ill patients he administers 1 gram of ascorbic acid intravenously daily or 100 mg intramuscularly at intervals of about two hours Infants require somewhat smaller doses for example 100 to 200 mg per day Within twenty four hours apathy listlessness weakness and the shock like state disappear and spontaneous bleeding is slackened In another day or two fever and bone and muscle pain abate During the ensuing few days the gums begin to heal and the perifollicular ecchymoses turn brown and then very slowly disappear Ecchymoses and deep hematomas gradually resorb and after several weeks the anemia

disappears Although some authors have recommended that hesperidin be given as well as ascorbic acid, there is no evidence that the bioflavinoids have any beneficial effect in patients with scurvy ACTH and corticosteroids are not of use Indeed, Stefanini and Rosenthal (638) have suggested that their administration may be deleterious the data obtained in experimental studies has been contradictory

SELECTED REFERENCES

66 Bicknell F and Prescott F *The Vitamins in Medicine* 3rd ed New York Grune & Stratton 1953

525 Ralli E P and Sherry S Adult scurvy and the metabolism of Vitamin C *Medicine* 20 251 1942

677 Vilter R W *Ascorbic Acid Effects of Deficiency in Human Beings* in *The Vitamins Chemistry Physiology Pathology* W H Sebrell Jr and R S Harris, edit New York Academic Press 1954

Chapter XXI

BENIGN PURPURAS OF UNKNOWN CAUSE

SIMPLE PURPURA

PROBABLY the commonest purpuric disorder is so mild in its manifestations that the patient usually seeks advice only for cosmetic reasons Spontaneous ecchymoses nearly always pain less and most frequently localized to the lower extremities occur in many otherwise healthy persons (194) I have called these lesions simple purpura unaware that this designation was used in the nineteenth century to describe petechial lesions The term "devil s pinches" may avoid this confusion

Nearly all the afflicted individuals who come to a physician s attention are women but this may merely reflect a feminine con cern with the appearance of the legs The patient usually states that she has bruised readily for as long as she can remember The ecchymoses are ordinarily painless but sometimes the larger lesions are tender to the touch New spots appear at irregular intervals unrelated to the menstrual cycle Each bruise lasts a few weeks and then disappears Often the patient says her skin is never free of bruises In some cases a new lesion is heralded by a stinging sensation suggesting the diagnosis of auto erythro cyte sensitization but readily distinguished from this disease by the absence of an urticarial element to the nascent lesion Occa sionally patients with simple purpura describe epistaxes menor rhagia or prolonged bleeding after tonsillectomy or dental ex traction These symptoms are sufficiently unusual that one doubts their relationship to the cutaneous manifestations Patients with simple purpura often state that the disturbance—it can hardly be called a disease—is present in their mother or daughters (151) Whether it is a genuinely hereditary disease is not clear

disappears Although some authors have recommended that hesperidin be given as well as ascorbic acid, there is no evidence that the bioflavinoids have any beneficial effect in patients with scurvy ACTH and corticosteroids are not of use Indeed, Stefanini and Rosenthal (638) have suggested that their administration may be deleterious, the data obtained in experimental studies has been contradictory

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66 Bicknell, F and Prescott F *The Vitamins in Medicine* 3rd ed New York Grune & Stratton 1953
525 Ralli E P and Sherry S Adult scurvy and the metabolism of Vitamin C *Medicine 20* 251 1942
677 Vilter R W *Ascorbic Acid Effects of Deficiency in Human Beings* in *The Vitamins Chemistry Physiology Pathology* W H Sebrell, Jr and R S Harris edit New York, Academic Press 1954

The essential nature of senile purpura is not clear Histologically the area in which senile purpura exists is characterized by an extreme degree of senile degeneration of the exposed skin (654) Individual lesions, then may be produced by minor external trauma acting on inadequately supported cutaneous blood vessels Presumably, blood leaks through the vessels into the skin (418 471) The bleeding seems to be more superficial than in the usual ecchymosis in which the extravasated blood spreads rather diffusely The intracutaneous injection of blood into normal individuals produces a lesion resembling senile purpura Harrington (264) pointed out that similar lesions may be seen in cachexia, and I have been impressed that the purpuric lesions of patients with Cushing s syndrome or under therapy with corticosteroids are sometimes similar in appearance (page 194) This similarity has led Scarborough and Shuster (573a) to suggest a common pathogenesis for senile and corticosteroid purpuras namely that in each situation the structure of cutaneous collagen is abnormal and that the normal inflammatory cellular response to extravasated blood is depressed

All tests of hemostatic function that have been applied to cases of senile purpura have been normal The prognosis is excellent since vital areas are not affected No therapy is indicated except reassurance of the patient

SELECTED REFERENCES

151 Davis E Hereditary familial purpura simplex. Review of 27 families *Lancet* 1 145 1941

152 Davis E Purpura of the skin A review of 500 cases *Lancet* 2 160 1943

654 Tattersall R N and Seville R Senile purpura *Quart J Med* n.s 19 151 1950

The fundamental defect responsible for the lesions of simple purpura is unknown A large number of individuals with this phenomenon have been studied at University Hospitals of Cleveland Tests of hemostatic function have been uniformly negative Although the presence of ecchymoses suggests that the cutaneous blood vessels are excessively fragile no data are available to support this conjecture Histologically Davis (152) observed microscopic extravasation of red blood cells without evidence of inflammation Fortunately, reassurance is the only therapy indicated

Unexplained ecchymoses similar in appearance to those of simple purpura, are observed in patients with Cushing's syndrome (264, 152) These lesions are probably directly related to the abnormalities in adrenal metabolism since similar lesions may be seen in patients under therapy with ACTH and corticosteroids (161, 359), particularly methylprednisolone and triamcinolone (397) Ecchymotic purpura has also been described in myxedema (419) and rheumatoid arthritis

SENILE PURPURA

Little attention has been paid in the literature to the cutaneous purpura characteristic of elderly people Tattersall and Seville (654) among the few who have studied senile purpura observed that its lesions occur with increasing frequency as individuals age In their experience, senile purpura was present in 2 per cent of patients in the seventh decade and 25 per cent of patients in the tenth decade of life The lesions are found on the extensor surface and radial border of the forearms on the back of the hand excluding the fingers, and rarely, along the area where eyeglass frames apply pressure to the face Each lesion is a large, irregular dark purple spot, about 1 to 4 cm in diameter with clear cut margins Each spot lasts for a period of days or many weeks and then leaves a residue of brownish pigmentation The skin of the affected areas is inelastic, thin and pigmented In these areas hair is scanty or absent Similar lesions can be reproduced within a few minutes by applying blunt pressure to the face or to the extensor surfaces of the forearm but not in other areas nor in the skin of patients without these lesions

turns brown and fades The urticarial wheal need not be fol lowed by a hemorrhagic lesion nor need the erythematous rash be preceded by urticaria The rash of anaphylactoid purpura is usually most evident on the lower extremities and the buttocks but the arms and lower trunk, and rarely the face may be in volved The extensor surfaces of the extremities are more often affected than the flexor surfaces At times localized edema forms on the back of the hands around the face eyes neck lips legs arms or penis In some cases an enanthem of petechial lesions may be present on the oral mucosa

Articular pain with or without swelling and tenderness is also common in anaphylactoid purpura The pain often seems disproportionate to the objective evidence of joint disease but is usually less intense than that of rheumatic fever One or more joints may be involved the pain and swelling often shifting from joint to joint Usually the swelling is clearly periarticular al though effusion into the joint may occur The wrists knees and ankles are the most frequently affected joints As Wedgwood and Klaus (700) emphasize heat redness and exquisite tenderness are conspicuously absent The articular pain and swelling last a few days and then recede but joint manifestations tend to recur repeatedly during the course of the illness Salicylates are with out obvious benefit Ultimately however complete recovery is the rule

A third major manifestation of anaphylactoid purpura is ab dominal pain present in about half of cases (453) Although the pain may be localized to any part of the abdomen it is most often periumbilical Each episode lasts a few days but the attacks tend to recur (7) The abdominal pain is usually severe and colicky in nature and may be accompanied by vomiting obstinate con stipation and such evidences of bleeding into the lumen of the gastrointestinal tract as melena frankly bloody stools or un commonly hematemesis The abdominal pain is thought to be initiated by edema or bleeding into the wall of the gastrointes tinal tract particularly in the region of the terminal ileum A palpable abdominal mass may be present The swollen gut wall may undergo intussusception particularly in children under the age of twelve resulting in gangrene and perforation of the in

Chapter XXII

ANAPHYLACTOID PURPURA

THE task of describing anaphylactoid, allergic or Henoch Schonlein's purpura is burdened by the absence of a specific test to establish the diagnosis, by the absence of a specific histologic lesion and by uncertainty about the fundamental nature of the illness Probably a response to a variety of stimuli, anaphylactoid purpura has been confused with such diseases as simple purpura, systemic lupus erythematosus polyarteritis nodosum rheumatic fever, acute glomerulonephritis autoerythrocyte sensitization and in an earlier era thrombocytopenic purpura

Anaphylactoid purpura is a systemic disease involving the skin and mucous membranes, the joints the gastrointestinal tract the kidneys the central nervous system and the heart Relatively common in children it is infrequent in adults in whom its course is often more protracted more benign and more confusing to the attending physician In children the disease occurs somewhat more often in boys than in girls

The onset of the illness is most variable (7, 153) Anaphylactoid purpura may begin with headache, anorexia or fever In other cases cutaneous manifestations, pains around the joints or abdominal complaints may be the first symptoms The rash usually symmetrical is found in almost every case and may take several forms Sometimes ecchymoses, varying in diameter from the size of a pinhead to several centimeters are the predominant lesion These ecchymotic lesions may be slightly raised and occasionally are tender The smallest intracutaneous hemorrhages may be petechial in character Hemorrhagic blebs or bullae may appear (126) In other cases the first cutaneous lesion is an urticarial wheal which evolves within hours into a pink maculopapule and in the following days to an ecchymosis which slowly

Asiatic influenzal vaccine (631) have been thought to induce the syndrome Sometimes in these drug induced cases petechial lesions often slightly elevated above the surrounding skin are the predominant lesion Often particularly in protracted cases in adults no offending agent can be discerned The possibility has been entertained on the basis of experiments in animals that anaphylactoid purpura may result from sensitization to the vascular endothelium (114, 299 57) but whether these observations are applicable to human disease is not known

The diagnosis of anaphylactoid purpura is based upon the presence of the principal clinical features—the rash arthralgia and gastrointestinal and renal symptoms The tourniquet test is sometimes positive (7) but other tests of hemostatic function are normal The white blood cell count is usually normal or only slightly elevated there may be mild eosinophilia The L E test is negative and the response to the intradermal injection of blood a test for autoerythrocyte sensitization has been normal in a few cases

A single episode of anaphylactoid purpura usually lasts no more than a few weeks but recurrent attacks occur in more than half of cases (153) Usually after several relapses each of which may have its own pattern of symptoms the disease disappears but sometimes the syndrome flares up repeatedly over many years Ackroyd (7) cites a case in which some sixty attacks occurred during a period of fifteen years Fatal cases are unusual death when it occurs may be attributable to the effects of nephritis intussusception or perforation of the inflamed intestinal wall.

Among the innumerable remedies which have been tried only ACTH and the corticosteroids have had any influence on the course of anaphylactoid purpura These agents sometimes abort the acute manifestations of the disease (639 339 635 359) My own experience similar to that of others (263) suggests that no fundamental benefit is derived from hormonal therapy The renal abnormalities are neither prevented nor ameliorated (493 699) and may indeed be intensified (698a) and recurrence of purpuric symptoms is not prevented Indeed in adults with chronic anaphylactoid purpura no therapeutic effect has been described from either brief or protracted courses of corticosteroids

testinal wall Steinhardt and Jones (641) point out the importance of early surgery whenever the diagnosis of intussusception is entertained, for delay may have serious consequences

Probably the most serious aspect of anaphylactoid purpura is the occurrence of renal damage (356) Gross or microscopic hematuria, proteinuria and hypertension are especially frequent in children over six years of age (700, 492) Although complete recovery is possible, microscopic hematuria, albuminuria and impaired renal function may persist for years and death from renal failure may result

About one fourth of patients with anaphylactoid purpura have a low-grade fever during the acute episode An occasional patient may have epistaxes or other evidences of a bleeding tendency including hemorrhage into the central nervous system (474) Unusually the tip of the spleen is palpable

The various clinical manifestations of anaphylactoid purpura are reflections of a widespread lesion in which the capillaries and arterioles are surrounded by polymorphonuclear lymphocytes, histiocytes and often eosinophiles The vascular walls may be completely necrotic (714) Collagen fibers in the vicinity of particularly intensive cellular infiltration may be swollen and stain poorly Microscopically in areas of petechiae and ecchymoses extravasated erythrocytes are seen in the neighborhood of affected vessels The epidermis or the mucosa of the intestinal tract may be edematous (225) The early renal lesions resemble those of systemic lupus erythematosus (675a) Later, the pathologic changes suggest subacute glomerulonephritis (698a)

Thus the histologic picture is consistent with the viewpoint that anaphylactoid purpura is an immune response similar as Osler believed, to serum sickness In many instances the disorder accompanies or follows within days after an infection, often by the beta hemolytic streptococcus but the lesions are not reminiscent of a pyogenic process In other cases, the syndrome seems to result from the ingestion of one or another drug antibiotic or food, the list of suspected agents is endless (264), including such common allergens as penicillin sulfonamides, salicylates, barbiturates, meprobamate (107), antihistaminic compounds and even corticosteroids (582) Mentholated cigarettes (284) and

Chapter XXIII

AUTOERYTHROCYTE SENSITIZATION

AUTOERYTHROCYTE sensitization a syndrome defined in 1955 by Gardner and Diamond (226) bears a superficial resemblance to anaphylactoid purpura The patients all adult women present a uniform picture (242 547 536) Each has had repeated crops of ecchymoses localized most often to the extremities Characteristically each lesion is heralded by a tingling or painful sensation which draws the patient s attention to the site Within minutes an itching urticarial erythematous palpable nodule appears which evolves during the next few hours into a tender and painful ecchymosis At times the ecchymosis seems to precede the urticaria and erythema but this is not the rule The center of each ecchymosis is often firm and nodular and is nearly always tender and painful After a week or two the ecchymoses gradually fade and disappear Sometimes new purpuric lesions are initiated by trauma and sometimes they appear spontaneously Associated with these episodes there may be abdominal pain often localized to the left upper quadrant where it is reminiscent of splenic infarction the spleen is not palpable Melena and hematuria have been described More ominously neurologic abnormalities such as hemiparesis or hemiplegia may appear sometimes leading to permanent brain damage It is noteworthy that four of the five patients I have seen have had severe incapacitating neuroses but this is not always the case

A typical case of autoerythrocyte sensitization occurred in a thirty seven year old housewife with severe hysteria who had had many surgical procedures during the preceding twelve years including an appendectomy bilateral mastectomy hysterectomy oophorectomy tonsillectomy dental extractions and three operations on her tempero-mandibular joints Two months

SELECTED REFERENCES

7 Ackroyd J F Allergic purpura including purpura due to food, drugs and infections *Am J Med 14* 605 1953
225 Gairdner D The Schonlein Henoch syndrome *Quart J Med n.s 17* 95 1948
700 Wedgwood R J P and Klaus M H Anaphylactoid purpura (Schonlein Henoch syndrome) A long term follow up study with special reference to renal involvement *Pediatrics 16* 196, 1955

normal reaction is seen in patients with simple purpura or typical Henoch Schonlein s purpura In patients with autoerythrocyte sensitization an erythematous wheal surrounds the site of injection within an hour or two and is followed within twenty four hours by a painful tender ecchymosis which is usually 3 to 5 cm in diameter but may attain a diameter of 15 to 20 cm It is probably wise not to repeat the test since it is distressing to the patient Needless to say only the patient s own blood should be used since the amount injected is many times greater than that needed to transmit the virus of infectious hepatitis from person to person In patients with the severest reaction even the intracutaneous injection of sterile solutions of isotonic sodium chloride will reproduce the lesion Perhaps in these cases the inevitable minute hemorrhage at the site of the injection initiates the abnormal response

Various forms of therapy have been attempted including splenectomy desensitization with the patient s own red cells and the administration of corticosteroids serum albumin rutin and estrogens The most that can be said is that remissions may occur after several years and caution should be exercised in attributing efficacy to any therapeutic agent The painful nature of the lesions has led to the use of analgesics and narcotics and one of the patients studied at University Hospitals of Cleveland has become addicted to Demerol

SELECTED REFERENCE

226 Gardner F H and Diamond L K Autoerythrocyte sensitization A form of purpura producing painful bruising following autosensitization to red blood cells in certain women Blood 10 675 1955

after an operation for the lysis of abdominal adhesions she first noted crops of ecchymoses on the legs and arms each preceded by about an hour by tingling itching a sensation of swelling and erythema The ecchymoses were tender and painful The patient had had intermittent tingling of the right arm since the last operation All tests of hemostatic function were normal. A tenth ml of the patient s own blood was injected intravenously Twenty four hours later a tender ecchymosis 2 x 5 cm in diameter, was present at the site of injection

Two years later new ecchymoses still appear at intervals of a week or more She has had many episodes of unconsciousness, believed to be part of a psychoneurotic conversion reaction Therapy directed at the purpuric lesions has been without benefit

The etiology of autoerythrocyte sensitization has been partially elucidated by Gardner and Diamond (226) In most cases the first symptoms appear shortly after an injury or surgical procedure For example, one of my patients was hit by a hand truck and another had been in an auto accident Gardner and Diamond wondered whether the patients became sensitive to their own erythrocytes as the result of the injury They demonstrated that the injection of the patient s venous blood into her own skin was followed by a replica of the typical lesion—urticaria erythema and a spreading painful ecchymosis The injection of the stroma of red cells was as effective as the injection of whole blood They suggested therefore that these patients react abnormally to their own red blood cells when these are extravasated into extravascular tissue On the other hand, intensive trials to demonstrate anti stromal antibodies in the serum of patients with autoerythrocyte sensitization have been unsuccessful (546a)

The reaction to the intracutaneous injection of blood can be used as a diagnostic test One tenth ml of blood is withdrawn from an antecubital vein through a number 24 gauge needle into a sterile tuberculin syringe and immediately injected intracutaneously into the anterior mid thigh The violaceous bleb which results is sharply circumscribed In normal individuals the bleb remains virtually unchanged for the next twenty four hours extending to an area about a centimeter in diameter, the purpuric spot closely simulates the lesion of senile purpura. The same

basic disease becomes evident with the passage of time but a few cases of each type remain unexplained The diagnosis of primary or essential hyperglobulinemia macroglobulinemia or cryoglobulinemia is an acknowledgment of the current limits to our understanding of the pathogenesis of these syndromes

The diagnosis of disturbances of the plasma proteins requires an awareness of the existence of these syndromes for the detec tion of cryoglobulins or macroglobulins is not an everyday pro cedure An increased concentration of globulin should raise the possibility that one of the three abnormalities may exist Appro priate tests will then lead to a more definitive diagnosis

PURPURA HYPERGLOBULINEMIA

Purpura hyperglobulinemia is a puzzling syndrome in which a characteristic hemorrhagic rash is associated with an abnor mally high concentration of gamma globulin in the serum First delineated by Waldenstrom (687) in 1943 purpura hyperglob ulinemia is probably not rare although only about seventy five cases have been reported Characteristically the disorder begins in early or mid adult life with the appearance of a hemorrhagic rash on the legs The lesion consists of small petechiae or minute ecchymoses ordinarily not more than 1 or 2 cm in diameter Sometimes the lesion begins with urticaria like swelling The rash gradually fades during the ensuing week or two only to be re- placed by a new crop of petechiae new lesions may be induced by bodily exertion (689) At first the petechiae disappear with out a trace but after months or years residual pigmentation not unlike that seen in stasis dermatitis accumulates At first the rash is confined to the legs but it gradually progresses to involve the skin of the thighs sometimes the lower trunk or abdomen and the arms

The pathologic changes observed in the skin of patients with purpura hyperglobulinemia have been reviewed by Hambrick (257) Within 12 hours after the appearance of a fresh lesion perivascular edema and infiltration with leukocytes and plasma cells are seen (586) Later there is microscopic necrosis of col lagen and fat around the blood vessels of the dermis Similar lesions are seen in the muscles of the legs along with destruc

Chapter XXIV

PURPURA ASSOCIATED WITH DYSPROTEINEMIA

OCCASIONALLY hemorrhagic phenomena may be related to qualitative or quantitative changes in the globulins of the circulating plasma These changes include hyperglobulinemia—any increase in the concentration of globulins cryoglobulinemia—the presence of proteins insoluble below body temperature and macroglobulinemia—the presence of globulins of unusually high molecular weight Each of these changes may be accompanied by a group of relatively stereotyped symptoms including evidences of a bleeding tendency However, the distinctions among the three groups are blurred for hyperglobulinemia may occur with either macroglobulinemia or cryoglobulinemia, and the macroglobulins frequently gel upon cooling, thus behaving as cryoglobulins Unfortunately, these considerations have often been overlooked in cases which have been reported

Although it is convenient to describe each of the three abnormalities separately it is likely that the pathogenesis of symptoms is partly common to all For example the viscosity of the blood may be increased if the concentration of globulin is elevated if macroglobulins are present in excess or, when the blood is cooled if there is cryoglobulinemia In turn the increased viscosity may decrease the blood flow through the capillaries impairing their nutrition Bleeding may occur as a consequence of the vascular damage Histologic evidence that the abnormal proteins may precipitate in the smallest blood vessels can be found in patients whose blood contains macroglobulins or cryoglobulins of normal molecular size

As several recent reviewers have stressed abnormalities in the serum proteins are themselves a reflection of disease rather than a primary disorder *sui generis* Nearly always the nature of the

unable to demonstrate antibodies against human aortic intima in the serum of his patient It is evident that further studies are needed before any firm conclusions can be drawn

No effective therapy for purpura hyperglobulinemia has been described Indeed were it not for the uncertain prognosis none would be indicated except for cosmetic purposes Splenectomy and corticosteroids have been tried without benefit

MACROGLOBULINEMIA

About 3 per cent of the proteins in normal plasma have a molecular weight of 1 000 000 or more These macroglobulins much heavier than other serum proteins are recognized by their rapid sedimentation when serum is subjected to ultracentrifugation Occasionally the concentration of these proteins of high molecular weight may be excessive This "macroglobulinemia" may be associated with such diverse conditions as cirrhosis nephrosis lymphosarcoma lymphatic leukemia myeloma or systemic lupus erythematosus There are however instances in which the alterations in serum proteins seem to form part of a distinctive syndrome This disorder "primary" macroglobulinemia was first delineated by Waldenstrom who has made many contributions to knowledge in this area (691 683)

Nearly all of the patients in whom macroglobulins have been demonstrated have been middle aged or elderly and many more cases have been reported in males than in females The patient usually comes to the physician only after months or years of gradually increasing weakness malaise lassitude and shortness of breath He may complain of ill defined abdominal pain or distress or anorexia Bleeding from mucous membranes particularly of the gingivae or nose is often an early and persistent symptom Blood may ooze from the nostrils intractably Less usually cutaneous bleeding—petechiae ecchymoses and protracted bleeding after injury—may occur as well as bleeding into the eye the central nervous system or the gastrointestinal tract or from the site of dental extractions Occasionally Raynaud s phenomena or tingling hyperesthesia or hypesthesia of hands or feet may be present

Pallor is often the most impressive feature of the physical

tion, disorganization and hyaline replacement of the muscular fibers

The etiology of purpura hyperglobulinemia is unknown Most of the cases have been in women many of whom seem free of other diseases For this reason the benign nature of this lesion has been stressed in the literature However an identical rash combined with elevation of serum gamma globulin has been described in patients with such disorders as Sjogren s syndrome, sarcoid, systemic lupus erythematosus unexplained arthritis and tuberculosis In one interesting case (360, 689), three of the patient s siblings had striking hypergammaglobulinemia without purpura, and two of these had lupus as well In Strauss' (646) patient the rash seemed to be accentuated after exposure to an insecticide In a patient observed at University Hospitals of Cleveland, the L E test was positive twenty two years after she first was aware of the rash This patient has had occasional arthralgia and unexplained episodes of fever, but other evidences of lupus have not yet appeared This patient s case points to the moral that one should be reserved about the prognosis of purpura hyperglobulinemia, for this syndrome may be the forerunner of serious disease

The pathogenesis of the purpura is unknown The gamma globulins are elevated from the normal concentration of about 1 0 to 1 5 grams per 100 ml to 2 5 grams or higher These gamma globulins are normal in size and do not precipitate upon cooling The concentration of albumin in serum is normal (689) No changes in the clotting mechanism have been reported but increased capillary fragility is often detectable (646) Hambrick (392) stressed the role of stasis believing that crops of petechiae follow prolonged standing or exertion He suggested that the vascular endothelium of the affected vessels is injured by the combination of stasis and the increased viscosity of the blood which results from the hyperglobulinemia In my own case, the rash on the legs has been much worse since the patient developed severe varicose veins Others have suggested that a normal globulin, required for the integrity of the vascular wall is absent from the plasma of these patients or that the vessel walls are injured by some hypersensitive reaction However Strauss (646) was

unable to demonstrate antibodies against human aortic intima in the serum of his patient It is evident that further studies are needed before any firm conclusions can be drawn

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Pallor is often the most impressive feature of the physical

examination In addition to any cutaneous manifestations of bleeding hemorrhages in the retina usually described as flame shaped may be seen Edema of the lower extremities is occasionally present In many cases enlargement of the lymph nodes liver or spleen may be noted, these organs are usually firm and are not tender Atrophy of the muscles seen in one of our patients, was described by Glenchur (235) The effects of hemorrhage into the central nervous system may be evident Bone tenderness is conspicuously absent

The *sine qua non* for establishing the diagnosis of macroglobulinemia is the demonstration by ultracentrifugation of serum proteins of abnormally high molecular weight The sedimentation constants of serum albumin and globulin are about 4 and 7 Svedburg units (S4 and S7) respectively Normally, about 3 per cent of serum proteins are macroglobulins of the S19 class with a molecular weight of about 1,000,000 In contrast 25 per cent or more of the serum protein of patients with macroglobulinemia may have sedimentation constants approximating S14 S19 or S25 all corresponding to proteins of high molecular weight Any given patient may have one or more types of macroglobulin and patients differ in the number and relative concentration of the various components present

Whether the macroglobulins are distinguishable from normal serum proteins by their antigenic characteristics is disputed (255 446) The macroglobulins break into smaller units upon the addition of sulfhydryl compounds as if they were aggregates of normal serum globulins of a molecular weight of about 160 000 polymerized by disulfide linkages (235 163) Moreover compared to normal serum proteins the macroglobulins are relatively rich in carbohydrate (171) This may help to explain the high viscosity of macroglobulinemic plasma Often the plasma of patients with macroglobulinemia gels when it is cooled the gelled protein may be separated by centrifugation at low temperatures Although cryoglobulins have been described in many of the reported cases it is likely that the supposed cryoglobulins were gelled macroglobulins (487)

The diagnosis of macroglobulinemia requires a high degree of awareness for ultracentrifugation is hardly a routine diagnostic procedure Waldenstrom emphasizes that an extremely

rapid erythrocyte sedimentation rate should raise the possibility that macroglobulins may be present However a normal sedimentation rate does not rule out the diagnosis for the excessive viscosity of the blood when it cools may slow sedimentation Nearly all patients have had an elevation of the serum globulins by ordinary salt fractionation techniques Analysis of the serum by paper electrophoresis usually discloses a single globulin peak of great intensity coincident with or close to the peak for gamma globulin

Laurell s modification of the Sia water test is helpful as a screening procedure for macroglobulinemia A liter cylinder is filled with distilled water A drop of serum is then layered over the surface of the water If the serum globulins are normal a cloud forms in the upper third of the cylinder but the turbidity quickly dissipates If the concentration of serum globulin is elevated a dense cloud appears in the upper and middle third of the cylinder and persists for some minutes If macroglobulins are present in excess a cloud forms in the middle third of the tube and coalesces into particles which drop rapidly to the bottom of the cylinder Other tests for the presence of abnormal proteins such as the cephalin cholesterol flocculation test the thymol turbidity test and the formol gel reaction are usually positive In one of my patients a weakly positive serologic test for syphilis had been noted several years before a false positive serologic test for syphilis has also been described by others

The patient with macroglobulinemia is usually a walking museum of hemorrhagic abnormalities Nearly always moderate or severe normochromic normocytic anemia is present The nature of this anemia is not clear Reticulocytosis sometimes provides evidence that the anemia is hemolytic The direct Coombs test has occasionally been positive (711) and autoagglutination of the erythrocytes has been described but the macroglobulins cause a clumping of red blood cells sharply increased by low temperatures so that these tests are difficult to interpret. The white blood cell count may be slightly increased normal or even decreased A relative lymphocytosis is the rule the peripheral blood smear may suggest that the patient has chronic lymphatic leukemia (727)

The bone marrow has been examined in most of the reported

cases Unless evidences of some other disease be found, the marrow is usually remarkable only in the presence of many cells which seem to represent a transition between lymphocytes and plasma cells These "lymphocytoid" cells as Waldenstrom (688, 690), described them, seem to have budding and shedding of their cytoplasm Mast cells may be present in great numbers In other cases, the marrow may seem entirely normal Occasionally, the urine contains Bence Jones protein The protein content of the cerebrospinal fluid may be elevated Hyperuricemia is occasionally present

X rays of the bones are usually normal, helping to distinguish macroglobulinemia from myeloma Occasionally, generalized decalcification may lead to compression fracture of the vertebrae (726), but usually no noteworthy changes are seen

The relationship between the macroglobulinemia and the nature of the patient s symptoms is puzzling Several patients have been described in whom symptoms were present prior to the appearance of macroglobulins in the peripheral blood (420) It seems nonetheless likely that many of the patient s symptoms are related to the great viscosity of the plasma No more than conjecture has been offered to explain such symptoms as dyspnea which is often disproportionate to the degree of anemia cyanosis or edema Perhaps one may invoke the abnormal viscosity of the blood with its attendant tissue anoxia as the cause of these symptoms

Studies to determine the cause of the bleeding tendency have produced a remarkable variety of findings (678 313) Thrombocytopenia may be prominent but this alone cannot account for the typically long bleeding time, which may be found in patients with normal platelet counts Sometimes the clotting time of whole blood is long particularly if it is measured in silicone coated tubes In different patients, decreased amounts of prothrombin or proaccelerin anticoagulant activity directed against the middle or last stages of clotting or abnormalities in the reactivity of fibrinogen to thrombin have been described Often the prothrombin consumption test reveals abnormalities in the earliest stages of clotting None of these findings adequately explains the bleeding tendency It seems likely that the macroglobulins in some way

impair the normal hemostatic function of the small blood vessels themselves perhaps because of their great viscosity The stimulus for the production of macroglobulins is entirely unknown Jim and Steinkamp (313) searched for a possible infectious agent without success

The prognosis of patients with macroglobulinemia is dependent upon the nature of any associated lesion In most cases the patients seem to survive for three or four years after the onset of symptoms Many types of therapy have been tried Although corticosteroids may occasionally induce remission (711 727) in most cases their effect is not impressive Urethane the nitrogen mustards and radio phosphorus have all been tried without success Splenectomy has been attempted but the results have not been spectacular (313 563) The possibility that the macroglobulins may be depolymerized by the administration of sulfhydryl compounds is intriguing (79) Usually life seems slowly to ebb away some infectious process may supply the finishing touch

CRYOGLOBULINEMIA

Cryogobulins are proteins which are less soluble than normal globulins so that they precipitate or gel when plasma is cooled below body temperature (361) The term encompasses a variety of abnormal proteins linked by this single characteristic Cryoglobulinemia may occur in association with a number of different diseases prominent among which are disturbances of the reticuloendothelial system (397) In some cases there may be symptoms which seem ascribable to the presence of these abnormal proteins The burgeoning literature concerning cryoglobulins has been reviewed repeatedly during the last few years (679 397 257, 725)

The classic clinical picture of cryoglobulinemia is exemplified by the earliest recognized case (716) The patient a fifty six year old woman with multiple myeloma noted a peculiar mottling of the arms and lower extremities and blueness of fingers toes the rims of the ears and the tip of the nose Shortly thereafter she observed coldness and blanching of the hands feet and tongue aggravated by cold or dampness Within the next month she experienced epistaxes dyspnea and palpitations The diagnosis of Raynaud s syndrome was made Retinal hemorrhages and dilata

tion of the retinal veins, suggestive of thrombosis of the central veins were present The patient also bled from the tongue and gums and had bruises of the extremities and abdomen, in addition to symptoms referable of the basic myelomatous process

Other symptoms may plague patients with cryoglobulinemia Urticaria may appear upon exposure to the cold, swimming seems to be a common incitant Itching is frequent (633) The extremities may be covered with a purpuric rash, usually petechial in nature hemorrhagic blisters which break down to form shallow ulcers may appear The hemorrhagic areas may extend over the entire body, particularly those regions exposed to cooling The individual lesions recede during the course of several days often leaving a residue of brownish pigmentation Blisters may also be found on the buccal mucosa

Other symptoms that have been described including vertigo or deafness perhaps due to the effects of cryoglobulinemia upon the inner ear abdominal pain, diarrhea or melena In a few cases, occlusion of the visceral or cerebral blood vessels has occurred and may be the immediate cause of death in fatal cases Gangrenous lesions of the tips of the fingers or toes or the helix of the ear may appear Swelling of the fingers ankles or other joints has been observed a sign which is probably due to whatever disorder underlies the cryoglobulinemia

A review of the characteristics of the cryoglobulins isolated from different patients indicates that a number of different types of these proteins may exist Broadly they can be divided into two groups, those in which the molecular weight approximates that of normal gamma globulin and those which are macroglobulins Without ultracentrifugal analysis, it is not possible to separate these two classes of cryoglobulins with certainty, although those with a normal molecular weight more often precipitate or flocculate when plasma is cooled below body temperature while the macroglobulins are more likely to gel This distinction is by no means absolute Cases of macroglobulinemia have been classified as such or as instances of cryoglobulinemia, depending upon the author s vantage point

The pathogenesis of the lesions in cryoglobulinemia is presumably related to the precipitation of these proteins in areas

exposed to temperatures at which these proteins precipitate The intravascular precipitates may then cause occlusion of blood vessels leading to petechiae and local areas of necrosis and gangrene (679) In one patient the administration of ergotamine a vasoconstrictor seemed to aggravate the purpuric rash (642) Histologically precipitated protein like material may be seen in these vessels sometimes surrounded by extravasated red blood cells and inflammatory perivascular changes Perhaps increased viscosity of the blood in the cooled areas contributes to the ischemia

Cryoglobulinemia may be associated with myriad diseases Cryoglobulins usually with a molecular weight resembling normal gamma globulin may be found in patients with multiple myeloma (690) lymphatic leukemia lymphosarcoma Hodgkin s disease systemic lupus erythematosus polyarteritis nodosum chronic "nephritis" subacute bacterial endocarditis Gaucher s disease Nieman Pick s disease and many other disorders (44) Often no symptoms seem attributable to the cryoglobulins and the correlation between the concentration of these abnormal proteins and the evidences of their presence is poor There is a residue of cases marked by exquisite sensitivity to cold urticarial purpuric vascular and gangrenous lesions of the skins and mucous membranes in which no underlying lesion can be found These cases bear a close resemblance to so called "allergy to the cold (488) Patients with such "essential" or "cryptogenic" cryoglobulinemia may have symptoms for years usually unaltered by our therapeutic efforts

Cryoglobulins should be looked for in any patient in whom exposure to the cold seems to precipitate or initiate symptoms (361 44) The presence of cryoglobulins should also be suspected when a specimen of venous blood appears to be abnormally viscous at room temperature Excessive rouleaux formation observed in smears of peripheral blood or reflected in a rapid sedimentation rate may also suggest the presence of cryoglobulins The concentration of serum globulin is not always elevated so that a normal concentration does not exclude the diagnosis Examination of aspirated bone marrow may reveal extensive vacuolization in the cytoplasm of the plasma cells (210) Since some of

the cryoglobulins may also be macroglobulins, a thorough study should include ultracentrifugal analysis of the patient's serum

Therapy for cryoglobulinemia, other than the avoidance of the cold, has been most unsatisfactory The usual gamut of hematologic remedies including corticosteroids and splenectomy, has been tried without striking benefit, only the use of Dicumarol suggested by Domz and Feigen (175), seems worthy of further testing

MULTIPLE MYELOMA

Hemorrhagic phenomena are common in patients with multiple myeloma but are usually of minimal importance in the course of this disease (531, 46, 218) Ecchymoses, petechiae, epistaxes, gingival bleeding, hematemesis, melena and bleeding from the site of wounds or surgical procedures have all been described (11 236), but only rarely is the bleeding of great severity (633)

The pathogenesis of bleeding in multiple myeloma is complex, and varies from patient to patient The changes which have been observed include thrombocytopenia (305 633) associated with a decrease in the number of megakaryocytes in the marrow Clot retraction may be impaired even in cases with a normal platelet count In other cases blood clotting may be delayed (531) and the formation of fibrin impaired (531, 221) a change manifested by the presence of an abnormally long thrombin time In some cases the alteration in the thrombin time is related to the presence of a circulating anticoagulant which interferes with the formation of fibrin (347 536), but such anticoagulants are only occasionally demonstrable (532)

Bleeding in multiple myeloma may also be associated with cryoglobulinemia, macroglobulinemia hyperglobulinemia amyloidosis and azotemia, all of which are commonly accompanied by a bleeding tendency Fortunately therapy for the bleeding tendency is seldom indicated since specific measures aimed at these various difficulties are not available

SELECTED REFERENCES

44 Barr D P Reader G L and Wheeler C H Cryoglobulinemia I Report of two cases with discussion of clinical manifestations incidence and significance *Ann Int Med* 32 6 1950

210 Firkin B G Essential Cryoglobulinemia *Am J Med 24* 974 1958
257 Hambrick, G Jr Dysproteinemic purpura of the hypergamma globulinemic type Clinical features and differential diagnosis *A M A Arch Derm 77* 23 1958
646 Strauss W G Purpura hyperglobulinemia of Waldenstrom Report of a case and review of the literature *New Eng J Med 260* 857 1959
689 Waldenstrom, J Three new cases of purpura hyperglobulinemia A study in long lasting benign increase in serum globulin *Acta Med Scand Suppl 266* 931 1952
691 Waldenstrom, J Macroglobulinemia, *Acta Haematologica 20* 33 1958
727 Zubrod, C G Hilbish T F Fahey J L Dutcher T F Fox, F A and Osserman, E F Waldenstrom s macroglobulinemia Clinical pathologic conference at the National Institutes of Health *Ann Int Med 50* 1010 1959

Chapter XXV

HEMORRHAGIC STATES COMPLICATING BLOOD TRANSFUSION AND THE USE OF EXTRACORPOREAL CIRCULATORY APPARATUS

ACUTE hemorrhagic symptoms in patients undergoing blood transfusion may be initiated by at least three mechanisms. Following the *transfusion of incompatible blood* the recipient may bleed severely at the sites of venipunctures or other parenteral injections, from any wounds, or after delivery, from the uterus. Muirhead (450) estimated that a bleeding tendency developed in a quarter of patients transfused with incompatible blood; the transfusion of as little as 100 ml. has been enough to initiate hemorrhage. Conley (116) demonstrated that the bleeding was at least partly the result of hypofibrinogenemia. In addition, there may be thrombocytopenia (343). Perhaps the hemolyzed erythrocytes release a clot promoting agent into the blood stream inducing intravascular clotting and defibrination (116, 517). Experimentally, the injection of hemolyzed blood produces a bleeding tendency (458), and incompatible blood transfusions reproduce to some extent the changes observed in patients (343, 394, 494). The treatment of the bleeding tendency is not clear. The intravenous injection of human fibrinogen seems reasonable. In one case, external bleeding stopped promptly after the intravenous injection of 3 gm. of this protein (504). Still, the possibility that the injected fibrinogen may clot intravascularly may give one pause until more experience has accumulated.

Bleeding may also occur as part of the syndrome which develops after the *transfusion of blood contaminated with bacteria* (337, 89). The passage of bloody stools is particularly characteristic (85). At autopsy, widespread evidence of petechial hemor

rhage is common However chills fever and signs of overwhelming shock dominate the clinical picture and the bleeding tendency is of minor importance

A hemorrhagic diathesis may also result after *massive blood transfusion* (337 636) This disorder was probably first described by *Bell* (51) *who reported that massive transfusions might result* in thrombocytopenia and deficiency of proaccelerin Krevans and his associates (337) observed severe thrombocytopenia in patients receiving ten or more liters of blood within a few hours This thrombocytopenia was nearly always associated with a hemorrhagic tendency characterized by the presence of petechiae ecchymoses bleeding from an operative site the mucous membranes the gastrointestinal tract or genitourinary tract Krevans (337) showed that each of five infants treated by exchange transfusion for erythroblastosis fetalis developed thrombocytopenia two of the five had hemorrhagic symptoms despite the use of fresh blood

The mechanism by which multiple transfusions result in thrombocytopena is not entirely clear Blood stored either in plastic or glass containers for more than 24 hours usually contains few or no platelets Those which remain survive only briefly after their transfusion Perhaps thrombocytopenia results from the dilution of the recipient s blood by this essentially platelet free blood Other possibilities must be explored

Thrombocytopenia may not account for all instances of bleed*ing after multiple transfusions In some patients who have re*ceived large amounts of blood traumatic or surgical wounds may ooze even though the platelet count remains normal (581 729) In these patients no one coagulative abnormality may be sufficient in itself to explain a bleeding tendency but multiple minor defects may be present which perhaps combine to produce a hemorrhagic state (729) In one of my patients there was a disturbance in the last stage of clotting manifested by a long thrombin time this patient also had severe thrombocytopenia

The treatment of the bleeding tendency of patients who have had multiple transfusions is difficult but prophylactic measures may be helpful The use of large amounts of blood or plasma should be avoided wherever possible If one can predict that a patient will need multiple transfusions freshly drawn blood

should be used in an attempt to delay the onset of thrombocy topenia

The infusion of dextran solutions, as a substitute for blood or plasma transfusions has occasionally been complicated by hem orrhage which may be of serious proportions (98) Various ex planations have been suggested to explain the adverse effect of the use of these agents In some subjects who have been trans fused with dextran solutions, the bleeding time may be prolonged (98), a defect which has been attributed to moderate thrombocy topenia (12) or to impairment of the function of the platelets (342) Such observations should serve as a reminder of the dangers attending the indiscriminate use of these blood sub-stitutes

The use of an *extracorporeal circulation* during cardiac surgery has occasionally been complicated by the oozing of blood from the operative wound Several studies (325 481, 681, 231) have indicated that cardiac by pass procedures may be accompanied by a fall in the concentration of fibrinogen a decrease in the platelet count, a slight increase in the rate at which clotted plasma lyses, and, in experimental animals a decrease in the concentra tion of antihemophilic factor Rarely, these abnormalities, and perhaps others as yet undetected are severe enough to cause a bleeding tendency (484) In addition, such patients are usually given intravenous injections of heparin to inhibit clotting while blood circulates through the extracorporeal oxygenator The treat ment of bleeding is two fold Transfusion with freshly drawn *blood may be used to replace lost blood if carefully drawn such* blood should not aggravate the patient s thrombocytopenia and should replace other factors which may be depressed If bleeding starts within four or five hours after heparin has been adminis tered the effect of the anticoagulant may be neutralized by the intravenous injection of 50 mg of protamine sulfate Ordinarily, larger doses should be avoided since protamine sulfate itself is an anticoagulant in the absence of heparin (484)

SELECTED REFERENCES

337 Krevans J R and Jackson D P Hemorrhagic disorder following massive whole blood transfusions *J.A.M.A* 159 171 1955

342 Langdell R D Adelson E Furth F W and Crosby W H Dextran and prolonged bleeding time Results of a 60 gram one liter infusion given to 163 normal human subjects *J A M A* *166* 346 1958
581 Scott R Jr and Crosby W H Changes in the coagulation mechanism following wounding and resuscitation with stored blood A study of battle casualties in Korea, *Blood* *9* 609 1954
681 von Kaulla K N and Swan H Clotting deviations in men during cardiac bypass Fibrinolysis and circulating anticoagulant *J Thoracic Surg* *36* 519 1958

Chapter XXVI

MISCELLANEOUS PURPURAS

HEMORRHAGIC SYMPTOMS WITH INFECTIOUS DISEASES

A LARGE number of infectious diseases may be accompanied by hemorrhagic manifestations unassociated with thrombocytopenia Petechial rashes are prominent features of meningococcal and rickettsial infections, subacute bacterial endocarditis and bacteremia due to many organisms The exanthem of scarlet fever is often petechial in the areas around the ankles and distal to any constriction by clothing a useful diagnostic sign In severe scarlet fever, the purpuric lesions may be extensive and there may be mucosal bleeding The rash in such other infections as measles, typhoid fever and small pox usually assumes hemorrhagic features only when the disease is severe In all these infections the hemorrhagic lesions have been attributed to vascular damage an explanation which seems to beg more fundamental issues The common statement that the purpuric cutaneous lesions observed in patients with bacteremia are due to infected microemboli seems to be conjectural

Rarely, in fulminant cases of meningococcal infection the rash takes on an ecchymotic character, some patients with this type of lesion may have the Waterhouse Friderichsen syndrome Cutaneous petechiae may be seen in cases of severe diphtheria the lesions have been ascribed to the action of diphtheria toxin Severe hemorrhage is also found in patients with Weil s disease or yellow fever In these diseases impaired synthesis of clotting factors may be more important than endothelial injury in the pathogenesis of the bleeding tendency

Thrombocytopenia with infection is discussed in Chapter XIV and purpura fulminans, a grave complication of many infections in Chapter IX

HEMORRHAGE DUE TO SNAKE VENOMS

At least four mechanisms have been proposed to explain the local and generalized bleeding which may follow snake bite Some venoms such as that of the North American rattlers are said to contain a "hemorrhagin" which destroys the endothelial lining of blood vessels Certain of the rattlesnakes have venom which is highly fibrinolytic their bite may produce bleeding because a stable clot cannot form The venom of the Russells viper contains a potent clot promoting agent which acts to accelerate the formation of thrombin Bleeding may follow the bite of this snake because the blood is defibrinated (327) The venom of the cobra or death adder on the other hand contains strong anticoagulant substances In addition the venom of such snakes may possess thrombin like activity which results in intravascular coagulation (383) The victim s blood then becomes incoagulable because the available fibrinogen has been converted to fibrin

AMYLOIDOSIS

In as many as one third of cases primary systemic amyloidosis is accompanied by signs of a bleeding tendency (191 283 571) Small cutaneous ecchymoses located most frequently in the folds of the axillae on and under the breasts in the groin and around the eyes are the commonest hemorrhagic manifestations Ecchymoses may also appear at sites of injuries sometimes a crop of purple spots form along the lines of a scratch There may be petechiae or blood filled vesicles the latter due to bleeding into the vesicular type of cutaneous amyloid lesion (238)

Bleeding may occur from any mucous membrane Gingival bleeding epistaxes the presence of petechiae or even ecchymoses on the oral mucosae petechiae in the rectal and sigmoid mucosae have all been described Hemorrhage vesicles on the tongue and gums have occasionally been responsible for massive bleeding Blood tinged sputum melena and even massive gastrointestinal bleeding have been observed. In one case the bleeding seemed to come from gastric erosions but no specific site of bleeding from the gastrointestinal tract is usually detectable

In most instances the hemorrhagic diathesis associated with primary amyloidosis is not associated with detectable alterations

in the blood clotting mechanism (571) Exceptionally, there may be hypofibrinogenemia (88), prolongation of the prothrombin time thrombocytopenia or a positive tourniquet test (264)

The most likely explanation for the hemorrhagic lesions associated with amyloidosis is that the blood vessels are infiltrated with amyloid Characteristic of this disease is widespread involvement of the smaller blood vessels and replacement of the media of the smallest arteries and arterioles by amyloid How this infiltration leads to rupture of the vessels and bleeding is not known (417) A similar explanation may account for the bleeding in secondary amyloidosis (60) The hemorrhagic symptoms of amyloidosis are usually unimportant from the point of view of prognosis, but an occasional patient will bleed to death as the result of gastrointestinal hemorrhage (60, 651) Specific therapy is not available for the treatment of this condition

PURPURA WITH RENAL FAILURE

Although they have received little attention, bleeding phenomena are extremely common in patients with renal failure, particularly in its terminal stages (528 340) Ecchymoses, subcutaneous hematomas petechiae epistaxis gingival and vaginal bleeding all occur, but are often ignored since more serious effects of azotemia dominate the clinical picture However, gastrointestinal or cerebral hemorrhage may be the immediate cause of death

Only recently have adequate studies been performed to determine the pathogenesis of the hemorrhagic tendency Perhaps because of the diversity of causes of renal failure there is little agreement concerning the responsible mechanisms In many patients, thrombocytopenia may contribute to bleeding (565, 340) but only in acute glomerulonephritis is it likely to be severe (528) In others, the platelets behave as if they were qualitatively defective failing to contribute normally to the formation of thromboplastin during coagulation (366) these alterations are reflected in abnormal prothrombin consumption" In still other patients, studies suggest the possibility that a circulating anticoagulant may be present In addition to these changes in the clotting mechanism the question remains unsettled whether vascular damage *per se* may be responsible for

the bleeding tendency (340) Finally, ulceration of the gastrointestinal tract has long been known as a source of gastrointestinal bleeding in azotemia whether these ulcerations are secondary to local hemorrhage is not known

Experimental studies have not explained the nature of the bleeding tendency in renal failure Gastrointestinal pulmonary and intracardiac bleeding have been observed in animals in experimental renal failure (370 452 184) The pathogenesis of bleeding in these animals is as obscure as in humans Mason (422) observed that the serum of uremic dogs is more proteolytic for fibrin than normal canine serum but there is no evidence that increased fibrinolysis is at the root of the hemorrhages in human cases Larrain and Langdell (345) observed prolongation of the clotting time of azotemic dog blood as measured in silicone coated tubes but they were unable to elucidate the mechanism With the increasing ability to control other manifestations of renal failure studies of the causes of bleeding are needed to permit rational therapy

SELECTED REFERENCES

191 Eisen H N Primary systemic amyloidosis *Am J Med 1* 144 1946
238 Goltz R W Systemized amyloidosis A review of the skin and mucous membrane lesions and a report of two cases *Medicine 31* 381 1952
366 Lewis J H Zucker M B and Ferguson J H Bleeding tendency in uremia *Blood 11* 1073 1956
383 McCreary J and Wurzel H Poisonous snake bites Report of case *J.A.M.A 170* 268 1959

BIBLIOGRAPHY

1 Aballi, A J Lopez Banus V de Lamerens S and Rozengvaig S Coagulation studies in the newborn period Alterations of thromboplastin generation and effects of Vitamin K in full term and premature infants *A.M.A J Dis Child 94* 589 1957

2 Achard C and Aynaud M Les globulins dans l anaphylaxie *Compt Rend Soc de biol 67* 83 1909

3 Ackroyd, J F The mechanism of the reduction of clot retraction by sedormid in the blood of patients who have recovered from sedormid purpura *Clin Sci 8* 235 1949

4 Ackroyd, J F The cause of thrombocytopenia in sedormid purpura *Clin Sci* 8 269 1949

5 Ackroyd J F Three cases of thrombocytopenic purpura occurring after rubella *Quart J Med* n s *18* 299 1949

6 Ackroyd J F The role of complement in sedormid purpura *Clin Sci 10* 185 1951

7 Ackroyd, J F Allergic purpura including purpura due to food, drugs and infections *Am J Med 14* 605 1953

8 Ackroyd, J F The role of sedormid in the immunological reaction that results in platelet lysis in sedormid purpura *Clin Sci* 13 409 1954

9 Adams E Postoperative thrombocytosis *Arch Int Med* 73 329 1944

10 Adams M A and Taylor F H L Thrombic activity of a globulin fraction of plasma proteins of beef swine and human blood, *Am J M Sc 205* 538 1943

11 Adams W S Allings E L and Lawrence J S Multiple myeloma Its clinical and laboratory diagnosis with emphasis on electrophoretic abnormalities *Am J Med 6* 141 1949

12 Adelson E Crosby W H and Roeder W H Further studies of a hemostatic defect caused by intravenous dextran *J Lab & Clin Med 45* 441 1955

13 Adelson E Rheingold J J and Crosby W H Studies of platelet survival by tagging *in vivo* with P^{32} *J Lab & Clin Med 50* 570 1957

14 Adelson, E and Roeder W H Studies on fibrinolysin using a

clinically practical method of quantitative determination *J Clin Path* *11* 82 1958
15 Aggeler P M Treatment of hemophilia *Blood* *11* 81 1956
16 Aggeler, P M and Lucia S P Neurologic complications of hemophilia *J Nerv Ment Dis* *99* 475 1944
17 Aggeler P M White S G Glendenning M B Page E W, Leake T B and Bates G Plasma thromboplastin component (PTC) deficiency a new disease resembling hemophilia *Proc Soc Exper Biol & Med* *79* 692 1952
18 Aggeler P M White, S G and Spaet, T H Deuterohemophilia Plasma Thromboplastin Factor B Deficiency Plasma thromboplastin component (PTC) deficiency Christmas disease hemophilia B *Blood* *9* 246 1954
19 Albrechtsen O K Storm O and Trolle, D Fibrinolytic activity in the circulating blood following amniotic fluid infusion *Acta haemat* *14* 309 1955
20 Aldrich R A Steinberg A G and Campbell D C Pedigree demonstrating a sex linked recessive condition characterized by draining ears eczematoid dermatitis and bloody diarrhea, *Ped* *13* 133 1954
21 Alexander B Antihemophilic principle of normal plasma, *J Clin Invest* *26* 1173 1947
22 Alexander, B Coagulation hemorrhage and thrombosis, *New Eng J Med* *252* 432 484 526 1955
23 Alexander B Clotting factor VII (proconvertin) Synonymy properties clinical and clinicolaboratory aspects *New Eng J Med* *260* 1218 1959
24 Alexander B de Vries A and Goldstein R Prothrombin activator in serum and its significance in certain hemorrhagic diseases *J Clin Invest* *27* 523 1948
✓ 25 Alexander B and Goldstein R Coagulation defect in hepatic disorders Deficiency of prothrombin conversion accessory substances *J Clin Invest* *29* 795 1950
26 Alexander B and Goldstein, R Parahemophilia in three siblings (Owren s disease) with studies on certain plasma components affecting prothrombin conversion, *Am J Med* *13* 255 1952
27 Alexander B and Goldstein R Dual hemostatic defect in pseudohemophilia *J Clin Invest* *32* 551 1953
28 Alexander B Goldstein R Landwehr G and Cook, C D Congenital SPCA deficiency A hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions *J Clin Invest* *30* 596 1951
29 Alexander B Goldstein R Rich L Le Bolloc'h, A G Diamond, L K and Borges W Congenital afibrinogenemia A study of some basic aspects of coagulation, *Blood* *9* 843 1954

30 Alexander B and Landwehr G Studies of hemophilia control of hemophilia by repeated infusions of normal human plasma *J A M A 138* 174 1948
31 Alexander B and Landwehr G Prothrombin consumption serum prothrombic activity and prothrombin conversion accelerator in hemophilia and thrombocytopenia *J Clin Invest* 28 1511 1949
32 Alexander B and Landwehr G Thrombasthenia and thrombocytopenic purpura Report of case demonstrating qualitative and quantitative inadequacy of platelets *New Eng J Med 241* 965 1949
33 Alexander B Meyers L Kenny J Goldstein R Gurewich V and Grinspoon L Blood coagulation in pregnancy Proconvertin and prothrombin and the hypercoagulable state *New Eng J Med 254* 358 1956
33a. Alfos L G Field E O and Ledlie E M Clinical studies with DF^{32}P on the lifespan of platelets *Lancet 2* 941 1959
34 Alkjaersig N and Seegers W H Formation of prothrombin from autoprothrombin by means of liver mitochondria *Am J Physiol 183* 111 1956
35 Allison A C Danger of Vitamin K to newborn *Lancet 1* 669 1955
36 Andreassen M K Haemofili i Danmark (Copenhagen E Munksgaard 1943) (Opera ex Domo biologiae hereditariae humanae Universitatis Hafniensis no 6 1943) (Copenhagen Theses 1943) [Engl summary]
37 Antes E H Thrombotic thrombocytopenic purpura A review of the literature with report of a case *Ann Int Med 48* 512 1958
38 Astrup T The biological significance of fibrinolysis *Lancet* 2 565 1956
38a Astrup T and Sjølin K E Thromboplastic and fibrinolytic activity of human synovial membrane and fibrous capsular tissue *Proc Soc Exp Biol & Med* 97 852 1958
39 Baehr G Klemperer P and Schifrin A An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thromboses of capillaries and arterioles *Trans Assoc Am Phys 51* 43 1936
40 Barbero G J Katz S and Kraus H Pathologic physiology in epidemic hemorrhagic fever *U S Armed Forces M J 4* 207 1953
41 Barbero G J Katz S Kraus H and Leedham C L Clinical and laboratory study of 31 patients with hemorrhagic fever *A M A Arch Int Med 91* 177 1953
42 Barnes A C Post partum blood Its clotting mechanism and relationship to peripheral blood picture *Am J M Sc 213* 463 1947
43 Barondess J A Thrombotic thrombocytopenic purpura Review of the literature and report of 3 cases *Am J Med 13* 294 1952
44 Barr D P Reader G G and Wheeler C H Cryoglobulinemia I

Report of two cases with discussion of clinical manifestations incidence and significance *Ann Int Med* 32 6 1950

45 Baserga A Arlotti, O and Ballerini, G Deux cas de thrombocythémie avec diathèse hémorragique au cours de la maladie de Vaquez *Le Sang* 28 218 1957

46 Bayrd E D and Heck, F J Multiple Myeloma A review of 83 proved cases, *J A M A* 133 147 1947

47 Bean W B *Vascular Spiders and Related Lesions of Skin* Springfield Charles C Thomas 1958

48 Beaumont J L Beaumont, V and Domart A Recherches sur l activité fibrinolytique spontanée du plasma dans les cirrhoses du foie *Rev Française d'Études Cliniques et Biologiques* 1 667 1958

49 Becker E Inactivation of Hageman factor by di isopropyl fluorophosphate DFP *J Lab & Clin Med* 56 136 1960

50 Bell W N A coagulation defect due to an anticoagulant possessing antithromboplastic and antithrombic properties probably heparin *Blood* 6 1199 1951

51 Bell, W N The clinical use of a coagulogram *Med Clin N America* 37 1843 1953

52 Bell W N *and Alton H G Brain extract as substitute for platelet* suspensions in thromboplastin generation test, *Nature* 174 880 1954

53 Bennike T and Mullertz S Haemorrhagic diathesis associated with fibrinogenopenia and fibrinolysis (a report of two cases) *Acta haemat* 8 147 1952

54 Bergsagel D E and Hougie C Intermediate stages in the formation of blood thromboplastin *Brit J Haemat* 2 113, 1956

55 Berlin C Urticaria Pigmentosa as a systemic disease *A M A Arch Derm* 71 703 1955

56 Berman L Axelrod A R Horan T N Jacobson S D, Sharp E A and VonderHeide E C The blood and bone marrow in patients with cirrhosis of the liver *Blood* 4 511 1949

57 Bernard J Le syndrome de Schonlein Henoch, *Rev d'hémat* 12 3 1957

58 Bernard J Beaumont, J L and Charreyron M Étude de la fonction thromboplastique des plaquettes dans deux cas de dystrophie thrombocytaire hémorragipáre congénitale *Rev d'hémat* 8 20 1953

59 Bernard J Caen J and Maroteau P La dystrophie thrombo cytaire hémorragipáre congénitale *Rev d'hémat* 12 222 1957

60 Bero G L Amyloidosis Its clinical and pathologic manifestations with a report of 12 cases *Ann Int Med* 46 931, 1957

61 Bethell F H Meyers M C Miller S and Bullock, W H Effects of ACTH and cortisone on idiopathic thrombocytopenic purpura, *Tr Ass Am Physicians* 64 199 1951

62 Bettelheim, F R and Bailey K Products of action of thrombin on fibrinogen *Biochim Biophys Acta* 9 578 1952
63 Bettex-Galland M and Lüscher E P Extraction of Actomysin like protein from human thrombocytes *Nature 184* 276 1959
64 Beveridge R S Haemorrhagic disease of the newborn *Arch Dis Childh* 3 39 1928
65 Biben, R L and Tyan, M L Hemorrhagic diathesis in carcinoma of the stomach A case report, *Ann Int Med 49* 917 1958
66 Bicknell, F and Prescott, F *The Vitamins in Medicine* 3rd ed New York, Grune & Stratton 1953
67 Bidwell, E Purification of antihemophilic globulin from animal plasma, *Brit J Haemat 1* 386 1955
68 Biggs R *Prothrombin Deficiency* Oxford Blackwell Scientific Publications 1951
68a. Biggs R Some observations on the blood of patients with "Factor VII" deficiency *Brit J Haemat* 2 412 1956
68b Biggs R Bidwell, E and Macfarlane R G The mode of action and aetiology of antihaemophilic globulin inhibitors *Sang 30* 340 1959
69 Biggs R and Douglas A S Thromboplastin generation test, *J Clin Path* 6 23 1953
70 Biggs R Douglas A S Macfarlane R G Dacie J V Pitney W R Merskey C and O'Brien, J R Christmas disease a condition previously mistaken for haemophilia *Brit M J* 2 1378 1952
71 Biggs R and Macfarlane R G *Human Blood Coagulation and Its Disorders* 2nd Edition Oxford, Blackwell Scientific Publications 1957
72 Biggs R and Macfarlane R G Haemophilia and related conditions *Brit J Haemat 4* 1 1958
73 Biggs R. Sharp A. A Margolis J Hardisty R. M Stewart, J and Davidson, W M Defects in the early stages of blood coagulation A report of four cases *Brit J Haemat 4* 177 1958
74 Birch, C. LaF Hemophilia—Clinical and genetic aspects *Illinois Medical and Dental Monographs Urbana* U of Illinois Press I No 4 1935-1937
75 Bird, R M Hammarsten, J F Marshall, R. A. and Robinson, R. R A family reunion A study of hereditary hemorrhagic telangiectasia, *New Eng J Med* 257 105 1957
76 Bird, R. M and Jaques W E Vascular lesion of hereditary hemorrhagic telangiectasia, *New Eng J Med 260* 597 1959
77 Bishop R. C Spencer H H and Bethell, F H Quinidine purpura Report of six cases *Ann Int Med* 50 1227 1959
78 Bjorkman, S E Three cases of polycythemia with fibrinopenia, *Acta Med Scand 129* 472, 1948

79 Bloch H S Prasad, A and Anastasi A Serum protein changes in Waldenstrom s macroglobulinemia during penicillamine administration *J Lab & Clin Med 52* 793 1958
80 Bolton F G Thrombocytopenic purpura due to quinidine II Serologic mechanisms *Blood 11* 547 1956
81 Bomford R R and Rhoads C P Refractory anaemia I Clinical and pathological aspects *Q J Med ns 10* 175 1941
82 Boon T H and Walton J N Aplastic anaemia *Q J Med ns 20* 75 1951
83 Borchgrevink, C F Egeberg O Pool J G Skulason T Stomorken H and Waaler B A study of a case of congenital hypoprothrombinaemia *Brit J Haemat* 5 294 1959
84 Borchgrevink C F Hellem A Voss D and Waaler B A Acquired hemorrhagic diathesis of unknown nature *Thromb diath Haem* 3 187 1959
85 Borden C W and Hall W H Fatal transfusion reactions from massive bacterial contamination of blood *New Eng J Med 245* 760 1951
86 Bordet J and Gengou O Réchèrches sur la coagulation du sang et les sérums anticoagulants *Ann Inst Pasteur 15* 129 1901
87 Born G V R Adenosine triphosphate (ATP) in blood platelets *Biochem J* 62 33 p 1956
88 Bowman H S Acquired fibrinogenopenia *Am J Med 24* 967 1958
89 Braude A I Transfusion reactions from contaminated blood Their recognition and treatment, *New Eng J Med 258* 1289 1958
89a Braude A I Brucellosis Disease a month Chicago Year Book Publishers 1957
90 Braunsteiner H and Pakesch F Thrombocytasthenia and thrombocytopathia—old names and new diseases *Blood 11* 965 1956
91 Brecher G and Cronkite E P *Estimation of the Number of Platelets by Phase Microscopy* in *The Coagulation of Blood Methods of Study* L M Tocantins Editor New York, Grune & Stratton 1955
92 Brink, A J and Kingsley C S Familial disorder of blood coagulation due to deficiency of labile factor *Q J Med ns 21* 19 1952
93 Brinkhous K M Study of clotting defect in hemophilia delayed formation of thrombin *Am J M Sc 198* 509 1959
94 Brinkhous K M and Graham J B Hemophilia in female dog, *Science 111* 723 1950
95 Brinkhous K M Smith H P and Warner E D Plasma prothrombin level in normal infancy and in hemorrhagic disease of the new born *Am J M Sc 193* 475 1937
96 Brinkhous K M Smith H P and Warner E D Prothrombin deficiency and the bleeding tendency in obstructive jaundice and in biliary fistula *Am J M Sc 196* 50 1938
97 Bronnimann, R. Kongenitale Afibrinogenämie Mitteilung eines Falles

mit multiplen Knochoncysten und Bildung eines Spezifischen Antikorpers (Antifibrinogen) nach Bluttransfusionen *Acta Haemat* *11* 41 1954

98 Bronwell A W Artz, C P and Sako Y Evaluation of blood loss from standardized wound after dextran *Surg Forum* *5* 809 1955

99 Budtz Olsen O E *Clot Retraction* Oxford, Blackwell Scientific Publications 1951

100 Burke H A Jr and Hartmann R C Thrombotic thrombocytopenic purpura—2 patients with remission associated with the use of large amounts of steroids *A M A Arch Int Med* *103* 105 1959

101 Burns J J Biosynthesis of L-Ascorbic Acid Basic defect in scurvy *Am J Med* *26* 740 1959

102 Caen J Déficit en facteur Hageman *Rev d'hémat* *13* 154 1958

103 Caen J and Bernard J Syndrome hémorrhagique dû au défaut du facteur prothromboplastinique de Rosenthal (P T A) *Le Sang* 27 249 1956

104 Calkins E Soodak, M and Bauer W Metabolism and clinical significance of the carbohydrate components of connective tissue *New Eng J Med* *253* 865 1955

105 Campbell J Hausler H R Munroe J S and Davidson I W F Effects of growth hormone in dogs *Endocrinology* *53* 134 1953

106 Capon N B Haemorrhagic disease of the new born a study of 61 cases *Lancet* *1* 431 1937

107 Carmel W J Jr and Dannenberg T Nonthrombocytopenic purpura due to Miltown (2 Methy 2 N propyl 1 3 propanediol dicarbamate) *New Eng J Med* *255* 770 1956

107a Carpenter A F Wintrobe M M Fuller E A Haut, A and Cartwright G E Treatment of idiopathic thrombocytopenic purpura, *J A M A* *171* 1911 1959

108 Cartwright G E *Diagnostic Laboratory Hematology* 2nd Edition New York, Grune and Stratton 1958

109 Chambers W N Holyoke J B and Wilson R F Purpura Fulminans Report of two cases following scarlet fever *New Eng J Med* *247* 933 1952

110 Chargaff E Bancroft F W and Stanley Brown M Studies on the chemistry of blood coagulation III The chemical constituents of blood platelets and their role in blood clotting with remarks on the activation of clotting by lipids *J Biol Chem* *116* 237 1936

111 Chevallier P Bernard, J Fiehrer A Bilski Pasquier G Samama M and Cerf M Deux cas d'hypoconvertinémie familiale *Sang* *26* 650 1955

112 Cho M H and Jaques L B Heparinase III Preparation and properties of the enzyme *Canad J Biochem Physiol* *34* 799 1956

113 Clark J F J and Ellison H S Hypofibrinogenemia associated with abortion a case report, *J Nat Med Assoc* *51* 54 1959

114 Clark W G and Jacobs, E Experimental non thrombocytopenic vascular purpura A review of the Japanese literature with preliminary confirmatory report *Blood 5* 320 1950
115 Clifford, S H Hemorrhagic disease of the newborn A critical consideration *J Ped 14* 333 1939
116 Conley, C L Symposium on use and misuse of blood transfusion in surgery Untoward reactions from blood transfusion, *Maryland M J 1* 547 1952
117 Conley, C L Disorders of the blood in disseminated lupus erythematosus *Am J Med 13* 1, 1952
118 Conley C L The blood in systemic lupus erythematosus *Bull Rheumat Dis 5* 87, 1955
119 Conley C L and Hartmann R C A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus *J Clin Invest 31* 621 1952
120 Conley, C L Hartmann R C and Morse W I II Circulating anticoagulants A technique for their detection and clinical studies *Bull Johns Hopkins Hosp 84* 255 1949
121 Conley C L Rathbun H K Morse W I II and Robinson J E Jr Circulating anticoagulant as a cause of hemorrhagic diathesis in man *Bull Johns Hopkins Hosp 83* 288 1948
122 *Conley C L Ratnoff O D, Ellicott, C E and Hartmann R C* Studies on the initiation of blood coagulation II An anticoagulant inhibiting the activation of a plasma thromboplastic factor *J Clin Invest 29* 1182 1950
123 Conley C L Ratnoff O D and Hartmann R C Studies on afibrinogenemia I Afibrinogenemia in a patient with septic abortion, acute yellow atrophy of the liver and bacteremia due to E coli, *Bull Johns Hopkins Hosp 88* 402 1950
124 Cooperberg A A and Neiman G M A Fibrinogenopenia and fibrinolysis in acute myelogenous leukemia *Ann Int Med 42* 706 1954
125 Cormier M J and Totter, J R Flavin mononucleotide-dependent menadione reductase coupled to cytochrome C reduction in cell free extracts of *Achromobacter fischeri J Am Chem Soc 76* 4744 1954
126 Craddock, C G Jr Adams W S Perry S and Lawrence J S The dynamics of platelet production as studied by a depletion technique in normal and irradiated dogs *J Lab Clin Med 45* 906 1955
127 Craddock C G., Jr., Fenninger L D and Simmons B Hemophilia problem of surgical intervention for accompanying diseases Review of literature and report of case *Ann Surg 128* 888 1948
128 Craddock, C G Jr and Lawrence J S Hemophilia Report of

mechanism of development and action of anticoagulant in 2 cases *Blood* 2 505 1947
129 Craddock, C G Jr Shotton, D Crockett, C L. and Leavell, B S Severe hypoprothrombinemia following propylthiouracil treatment of thyrotoxicosis *New Eng J Med 244* 549 1951
130 Craig, J M and Gitlin, D The nature of the hyaline thrombi in thrombotic thrombocytopenic purpura, *Am J Path* 33 251 1957
131 Crandon J H Lund, C C and Dill, D B Experimental human scurvy *New Eng J Med 223* 353 1940
132 Cronkite E P The hemorrhagic syndrome of acute ionizing radiation illness produced in goats and swine by exposure to the atomic bomb at Bikini, 1946 *Blood 5* 32 1950
133 Curtis G M and Movitz, D The surgical significance of the accessory spleen *Ann Surg 123* 276 1946
134 Cutforth, R H Adult scurvy *Lancet 1* 454 1958
135 Dacie J V *The Haemolytic Anaemias Congenital and Acquired,* Grune & Stratton New York, 1954
136 Dalldorf G A sensitive test for subclinical scurvy in man, *Am J Dis Child 46* 794 1933
137 Dam, H Hemorrhages in chicks reared on artificial diets A new deficiency disease *Nature 133* 909 1934
138 Dam H Dyggve H Larsen H and Plum, P The relation of Vitamin K deficiency to hemorrhagic disease of the newborn, *Adv Ped 5* 129 1952
139 Dam, H and Schønheyder F The occurrence and chemical nature of Vitamin K, *Biochem J* 30 897 1936
140 Dam, H Schønheyder F and Tage Hansen, E Studies on the mode of action of Vitamin K, *Biochem J 30* 1075 1936
141 Dam, H Tage Hansen, E and Plum, P Vitamin K lack in normal and sick infants *Lancet 2* 1157 1939
142 Dameshek, W A method for the simultaneous enumeration of blood platelets and reticulocytes *Arch Int Med 50* 579 1932
143 Dameshek, W Systemic lupus erythematosus A complex autoimmune disorder *Ann Int Med 48* 707 1958
144 Dameshek, W and Miller E B The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism, *Blood 1* 27 1946
145 Dameshek, W and Reeves W H Exacerbation of lupus erythematosus following splenectomy in "idiopathic" thrombocytopenic purpura and auto-immune hemolytic anemia, *Am J Med 21* 560 1956
146 Dameshek, W and Rheingold, J J Idiopathic thrombocytopenic purpura and menorrhagia mistakenly treated for local disease Report of 4 cases J.A.M.A 139 993 1949

114 Clark, W G and Jacobs, E Experimental non thrombocytopenic vascular purpura A review of the Japanese literature with preliminary confirmatory report *Blood 5* 320 1950
115 Clifford S H Hemorrhagic disease of the newborn A critical consideration *J Ped 14* 333 1939
116 Conley C L Symposium on use and misuse of blood transfusion in surgery Untoward reactions from blood transfusion, *Maryland M J 1* 547 1952
117 Conley C L Disorders of the blood in disseminated lupus erythematosus *Am J Med 13* 1 1952
118 Conley C L The blood in systemic lupus erythematosus *Bull Rheumat Dis 5* 87 1955
119 Conley C L and Hartmann R C A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus *J Clin Invest 31* 621 1952
120 Conley, C L, Hartmann R C and Morse W I II Circulating anticoagulants A technique for their detection and clinical studies *Bull Johns Hopkins Hosp 84* 255 1949
121 Conley C L Rathbun H K Morse W I II and Robinson, J E Jr Circulating anticoagulant as a cause of hemorrhagic diathesis in man *Bull Johns Hopkins Hosp 83* 288 1948
122 Conley C L Ratnoff O D Ellicott C E and Hartmann, R C Studies on the initiation of blood coagulation II An anticoagulant inhibiting the activation of a plasma thromboplastic factor *J Clin Invest 29* 1182 1950
123 Conley C L Ratnoff O D and Hartmann, R C Studies on afibrinogenemia I Afibrinogenemia in a patient with septic abortion, acute yellow atrophy of the liver and bacteremia due to E coli, *Bull Johns Hopkins Hosp 88* 402 1950
124 Cooperberg A A and Neiman G M A Fibrinogenopenia and fibrinolysis in acute myelogenous leukemia *Ann Int Med 42* 706 1954
125 Cormier M J and Totter J R Flavin mononucleotide-dependent menadione reductase coupled to cytochrome C reduction in cell free extracts of *Achromobacter fischeri J Am Chem Soc 76* 4744 1954
126 Craddock, C G Jr Adams W S Perry S and Lawrence J S The dynamics of platelet production as studied by a depletion technique in normal and irradiated dogs *J Lab Clin Med 45* 906 1955
127 Craddock, C G Jr Fenninger L D and Simmons B Hemophilia problem of surgical intervention for accompanying diseases Review of literature and report of case *Ann Surg 128* 888 1948
128 Craddock, C G Jr and Lawrence, J S Hemophilia Report of

mechanism of development and action of anticoagulant in 2 cases *Blood* 2 505 1947
129 Craddock, C G Jr Shotton, D., Crockett, C L and Leavell B S Severe hypoprothrombinemia following propylthiouracil treatment of thyrotoxicosis *New Eng J Med* 244 549 1951
130 Craig J M and Gitlin D The nature of the hyaline thrombi in thrombotic thrombocytopenic purpura, *Am J Path* 33 251 1957
131 Crandon, J H Lund, C C and Dill, D B Experimental human scurvy *New Eng J Med* 223 353 1940
132 Cronkite E P The hemorrhagic syndrome of acute ionizing radiation illness produced in goats and swine by exposure to the atomic bomb at Bikini, 1946 *Blood* 5 32, 1950
133 Curtis G M and Movitz, D The surgical significance of the accessory spleen *Ann Surg* 123 276 1946
134 Cutforth, R. H Adult scurvy *Lancet* 1 454 1958
135 Dacie J V *The Haemolytic Anaemias Congenital and Acquired* Grune & Stratton, New York, 1954
136 Dalldorf G A sensitive test for subclinical scurvy in man, *Am J Dis Child* 46 794 1933
137 Dam, H Hemorrhages in chicks reared on artificial diets A new deficiency disease *Nature* 133 909 1934
138 Dam, H., Dyggve H Larsen, H and Plum, P The relation of Vitamin K deficiency to hemorrhagic disease of the newborn, *Adv Ped* 5 129 1952
139 Dam, H and Schønheyder F The occurrence and chemical nature of Vitamin K, *Biochem J* 30 897 1936
140 Dam, H Schønheyder F and Tage-Hansen, E Studies on the mode of action of Vitamin K, *Biochem J* 30 1075 1936
141 Dam, H Tage-Hansen E and Plum, P Vitamin K lack in normal and sick infants *Lancet* 2 1157 1939
142 Dameshek, W A method for the simultaneous enumeration of blood platelets and reticulocytes *Arch Int Med* 50 579 1932
143 Dameshek, W Systemic lupus erythematosus A complex autoimmune disorder *Ann Int Med* 48 707 1958
144 Dameshek, W and Miller E B The megakaryocytes in idiopathic thrombocytopenic purpura a form of hypersplenism, *Blood* 1 27 1946
145 Dameshek, W and Reeves W H Exacerbation of lupus erythematosus following splenectomy in "idiopathic" thrombocytopenic purpura and auto-immune hemolytic anemia, *Am J Med* 21 560 1956
146 Dameshek, W and Rheingold, J J Idiopathic thrombocytopenic purpura and menorrhagia mistakenly treated for local disease Report of 4 cases *J.A.M.A* 139 993 1949

114 Clark, W G and Jacobs E Experimental non thrombocytopenic vascular purpura A review of the Japanese literature with preliminary confirmatory report *Blood 5* 320 1950

115 Clifford, S H Hemorrhagic disease of the newborn A critical consideration *J Ped 14* 333 1939

116 Conley, C L Symposium on use and misuse of blood transfusion in surgery Untoward reactions from blood transfusion *Maryland M J 1* 547 1952

117 Conley C L Disorders of the blood in disseminated lupus erythematosus *Am J Med 13* 1 1952

118 Conley C L The blood in systemic lupus erythematosus *Bull Rheumat Dis 5* 87 1955

119 Conley C L and Hartmann R C A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus *J Clin Invest 31* 621 1952

120 Conley C L Hartmann R C and Morse W I II Circulating anticoagulants A technique for their detection and clinical studies *Bull Johns Hopkins Hosp 84* 255 1949

121 Conley C L Rathbun H K Morse W I II and Robinson, J E Jr Circulating anticoagulant as a cause of hemorrhagic diathesis in man *Bull Johns Hopkins Hosp* 83 288 1948

122 Conley C L, Ratnoff O D Ellicott, C E and Hartmann R. C Studies on the initiation of blood coagulation II An anticoagulant inhibiting the activation of a plasma thromboplastic factor *J Clin Invest 29* 1182 1950

123 Conley C L Ratnoff O D and Hartmann R C Studies on afibrinogenemia I Afibrinogenemia in a patient with septic abortion acute yellow atrophy of the liver and bacteremia due to E coli, *Bull Johns Hopkins Hosp 88* 402 1950

124 Cooperberg A A and Neiman G M A Fibrinogenopenia and fibrinolysis in acute myelogenous leukemia, *Ann Int Med 42* 706 1954

125 Cormier M J and Totter, J R Flavin mononucleotide-dependent menadione reductase coupled to cytochrome C reduction in cell free extracts of *Achromobacter fischeri J Am Chem Soc 76* 4744 1954

126 Craddock, C G Jr Adams W S Perry S and Lawrence, J S The dynamics of platelet production as studied by a depletion technique in normal and irradiated dogs *J Lab Clin Med 45* 906 1955

127 Craddock, C G Jr., Fenninger L. D and Simmons B Hemophilia problem of surgical intervention for accompanying diseases Review of literature and report of case *Ann Surg 128* 888 1948

128 Craddock, C G Jr and Lawrence J S Hemophilia Report of

166 Diamond L. K. and Porter F S The inadequacies of routine bleeding and clotting times *New Eng J Med 259* 1025 1959

167 Didisheim P Ferguson J H and Lewis J H Hemostatic data in relatives of hemophiliacs A and B *A M A Arch Int Med 101* 347 1958

168 Didisheim P and Lewis J H *Congenital disorders of the mechanism for coagulation of blood Ped* 22 478 1958

169 Didisheim, P Loeb J Blatrix C and Soulier J P Preparation of a human plasma fraction rich in prothrombin proconvertin Stuart factor and PTC and a study of its activity and toxicity in rabbits and man *J Lab Clin Med* 53 322 1959

170 Dieckmann W J Blood chemistry and renal function in abruptio placentae *Am J Obst & Gyn 31* 734 1936

171 Di Guglielmo R and Antoninx, F M Contribution a la connaissance de la macroglobulinémie de Waldenstrom *Sang* 26 249 1955

172 Dische F E and Benfield V Congenital factor VII deficiency Hematological and genetic aspects *Acta Haemat 21* 257 1959

173 Doan, C A The etiology and management of the hemorrhagic diatheses *Ann Int Med* 31 967 1949

174 Dolin M I The flavin requirement for DPNH menadionereductase in *Streptococcus faecalis Biochim et Biophys Acta 15* 153 1954

175 Domz, C A and Feigen E V Cryoglobulinemia Rationale and results of bishydroxycoumarin (Dicumarol) therapy *A M A Arch Int Med 100* 471 1957

176 Donaldson V H The effect of plasmin *in vitro* on clotting factors in plasma *J Lab Clin Med* (in press)

177 Douglas A S Factor V consumption during blood coagulation *Brit J Haemat 2* 153 1956

178 Douglas A S Antihemophilic globulin consumption during blood coagulation *Blood 11* 423 1956

179 Douglas A S The action of heparin in the prevention of prothrombin conversion *J Clin Invest 35* 533 1956

180 Douglas A S Some observations on the coagulation defect in Vitamin K deficiency *J Clin Path 11* 261 1958

181 Douglas A S and Davies P Hypoprothrombinemia in the newborn *Arch Dis Childhood* 30 509 1955

182 Douglas A S and McAlpine S G Neurologic complications of haemophilia and Christmas disease *Scottish M J 1* 270 1956

183 Doyon M Incoagulabilité du sang provoquée par le chloroforme rôle du foie *Compt rend soc de biol* 58 30 1905

184 Drury D R The production by a new method of renal insufficiency and hypertension in the rabbit *J Exptl Med* 68 693 1938

185 Dubois E L Methyl prednisolone (Medrol) in the treatment of systemic lupus erythematosus *J.A M.A 170* 1537 1959

186 Duff I. F Gamble J R Willis P W III Hodgson P E Wilson,

147 Dameshek, W Rubio F Jr Mahoney J P Reeves W H and Burgin L A Treatment of idiopathic thrombocytopenic purpura (ITP) with prednisone *J A M A 166* 1805 1958

148 Dausset J Delafontaine P and Fleuriot Y Agglutination et destruction *in vitro* des plaquettes normales par le sérum d une malade atteinte de purpura thrombopénique aigu Inhibition par ce sérum de la retraction du caillot normal *Sang 23* 373 1952

149 Davidson C S Hemophilia Clinical study of 40 patients *Blood 4* 97 1949

150 Davie E W and Ratnoff O D Unpublished Observations

151 Davis E Hereditary familial purpura simplex Review of 27 families *Lancet 1* 145 1941

152 Davis E Purpura of the skin A review of 500 cases *Lancet 2* 160 1943

153 Davis E The Schonlein Henoch syndrome of vascular purpura, *Blood 3* 129 1948

154 Davis F W Genecin A and Smith E W Gauchers disease with thrombocytopenia an instance of selective hypersplenism *Bull Johns Hopkins Hosp 83* 176 1949

155 Dawson J P Congenital pancytopenia associated with multiple congenital anomalies (Fanconi type) Review of the literature and report of a 20 year old female with a 10 year follow up and apparently good response to splenectomy *Ped 15* 325 1955

156 Delcroix R M Etude statistique de 1 062 cas de syndromes hémorrhagiques Thesis *Faculté de Médecine* Paris 1958

157 de Nicola P Factor VII (SPCA) Its physiopathologic significance *Blood 8* 947 1953

158 de Nicola P *The Laboratory Diagnosis of Coagulation Defects* Springfield Charles C Thomas 1956

159 de Nicola P *Thromboelastography* Springfield, Charles C Thomas 1957

160 de Nicola P and Fumarola D Richerche sul difetto emostatico da somministrazione di antimitotici e antimetaboliti nell animale *Giornale Italiano di Chemioterapia 2* 168 1955

161 Denko C W and Schroeder L R Ecchymotic skin lesions in patients receiving prednisone *J A M A 164* 41 1957

162 De Palma A F and Cotler J Hemophilic arthropathy *Clin Orthop 8* 163 1956

163 Deutsch H F and Morton J L Dissociation of human serum macroglobulins *Science 125* 600 1957

164 de Vries A and Izak G Thrombocytopenic purpura without anemia and leucopenia in Gauchers disease *Blood 10* 1055 1955

165 de Vries A Shafrir E Efrati P and Shamir Z Thrombocytopathic purpura with normal prothrombin consumption Hemorrhagic diathesis due to partial platelet dysfunction *Blood 8* 1000 1953

tion of plasma antithrombin activities *Proc Soc Exper Biol. & Med.* *85* 199 1954
203a Ferguson A W Rubella as a cause of thrombocytopenic purpura, *Ped* *25* 400 1960
204 Ferguson, J H Johnston, C L Jr and Howell D A A circulating inhibitor (Anti AcG) specific for the labile Factor V of the blood clotting mechanism *Blood* 13 382, 1958
205 Ferguson R. H Sarcoidosis Study of 29 cases with a review of splenic hepatic mucous membrane retinal and joint manifestations *A M.A. Arch Int Med.* *101* 1065 1958
206 Ferry J D Miller M and Shulman, S Conversion of fibrinogen to fibrin rigidity and stress relaxation of fibrin clots effect of calcium *Arch Biochem.* *34* 424 1951
207 Ferry J D and Morrison P R Preparation and properties of serum and plasma proteins VIII The conversion of human fibrinogen to fibrin under various conditions *J Am Chem Soc* 69 388 1947
208 Figi, F A and Watkins C H Hereditary hemorrhagic telangiectasia *Proc Staff Meet Mayo Clinic* *18* 418 1943
209 Finkbiner R. B McGovern J J Goldstein, R and Bunker J P Coagulation defects in liver disease and response to transfusion during surgery *Am J Med* *26* 199 1959
210 Firkin, B C Essential Cryoglobulinemia *Am J Med* *24* 974 1958
211 Fisher E R. and Creed D L. Thrombotic thrombocytopenic purpura Report of a case with discussion of its tinctoral features *Am J Clin Path* *25* 620 1955
212 Fitch, H J An explanation of the discrepancy between direct and indirect platelet counts *Blood* *12* *671* 1957
212a Flute P T and Howard A. N Blood coagulation in scorbutic guinea pigs A defect in activation by glass contact, *Brit J Haemat* 5 421 1959
213 Follis R H Jr Maldevelopment of the corium in the osteogenesis imperfecta syndrome *Bull Johns Hopkins Hosp* *93* 225 1953
214 Follis R. H Jr Park, E A. and Jackson, D The prevalence of scurvy at autopsy during the first two years of age *Bull Johns Hopkins Hosp* *87* 569 1950
215 Foster D P and Whipple G H Blood fibrin studies II Normal fibrin values and the influence of diet, *Am. J Physiol* *58* 379 1921
216 Fountain, J R Haemorrhagic thrombocythaemia Report of two cases treated with radioactive phosphorus *Brit M J 2 126 1958*
216a Fountain J R and Holman, R L Acquired fibrinogen deficiency associated with carcinoma of the bronchus *Ann Int Med* *52* 459 1960
217 Fowler W M Thrombopenic purpura an analysis of 160 cases *Ann. Int Med* 9 1475 1936

W S and Polhemus, J A. The control of excessive effect by anti coagulants *Ann Int Med 43* 955 1955
187 Duke W W The relation of blood platelets to hemorrhagic disease Description of a method for determining the bleeding time and coagulation time and report of 3 cases of hemorrhagic disease relieved by transfusion *J A M A 55* 1185 1910
188 Dyggve H A case of purpura fulminans with fibrinogenopenia in association with scarlatina *Acta Med Scandinav 127* 382 1947
189 Dyggve H Prothrombin and proconvertin in the newborn and during the first year of life *Acta Paediat 47* 251 1958
190 Ehrlich L and Schwartz S O Splenomegaly in thrombocytopenic purpura, *Am J Med Sci 221* 158 1951
191 Eisen H N Primary systemic amyloidosis *Am J Med 1* 144 1946
192 Emery J L Gordon R R, Rendle Short J Varadi S and Warrack, A J N Congenital amegakaryocytic thrombocytopenia with congenital deformities and a leukemoid blood picture in the newborn *Blood 12* 567 1957
193 *Epstein, R D Lozner E L Cobbey T S Jr* and *Davidson, C S* Congenital thrombocytopenic purpura *Am J Med 9* 44 1950
194 Estren S Medal L S and Dameshek W Pseudohemophilia, *Blood 1* 504 1946
195 Evans R S Takahashi K Duane R T Payne R and Liu C K Primary thrombocytopenic purpura and acquired hemolytic anemia *A M A Arch Int Med 87* 48 1951
196 Evans T S The spleen and thrombocytopenic purpura *Le Sang 26* 145 1955
197 Fahey J L, Ware A G and Seegers W H Stability of prothrombin and *Ac globulin in stored human plasma as influenced by conditions of storage Am J Physiol 154* 122 1948
198 Fanger H Cella L J Jr and Litchman H Thrombocythemia. A report of 3 cases and review of literature *New Eng J Med 250* 456 1954
199 Fantl P *Parahemophilia (Proaccelerin Deficiency) Occurrence and Biochemistry in Hemophilia and Hemophilioid Diseases* K Brinkhous edit *Chapel Hill, U of N Carolina Press 1957*
200 Fantl P and Simon S E Fibrinolysis following electrically induced convulsions *Australian J Exp Biol Med Med Sci 26* 521 1948
201 Favre Gilly J Normand J Guillot, A. Thouvérez, J P Conin Alane and Froment R Diathèse hémorrhagique par héparinémie avec thrombocytopénie au cours d une polyérythémato-viscérite *Lyon Med 90* 981 1958
202 *Fearnley G R. and Bunim J J Effect of ACTH on the erythrocyte*-sedimentation rate and plasma fibrinogen and serum protein levels in normal persons *Lancet 2* 1113 1951
203 Fell, C., Ivanovic, N Johnson S A and Seegers W H Differentia

Beitrag zur Pathologie der Blutplattchen *Jb Kinderheilk 88* 113 1918
235 Glenchur H Zinneman H H and Briggs D R Macroglobulinemia Report of two cases *Ann Int Med 48* 1055 1958
236 Glenchur H Zinneman H H and Hall, H W A review of 51 cases of multiple myeloma Emphasis on pneumonia and other infections as complications *A M A Arch Int Med 103* 173 1959
237 Gofstein R and Gellis S S Splenectomy in infancy and childhood The question of overwhelming infection following operation *A M A J Dis Child 91* 566 1956
237a Gollub S Ulin A Paxson N F Winchell H S O Riordan J Back, N and Ambrus J L Obstetric hemorrhage in criminal abortion and abruptio placentae A study of blood coagulation and fibrinolytic systems in three cases *J Lab Clin Med* 53 765 1959
238 Goltz, R W Systemized amyloidosis A review of the skin and mucous membrane lesions and a report of two cases *Medicine* 31 381 1952
239 Good T A Carnazzo S F and Good R A Thrombocytopenia and giant hemangioma in infants *A M A J Dis Child 90* 260 1955
240 Goodpasture E W Fibrinolysis in chronic hepatic insufficiency *Bull Johns Hopkins Hosp 25* 330 1914
241 Gothlin G F Outline of a method for the determination of the strength of the skin capillaries and the indirect estimation of the individual Vitamin C standard *J Lab Clin Med 18* 484 1933
242 Gottlieb P M Stupniker S Sandberg H and Woldow I Erythrocyte autosensitization *Am J M Sc* 233 196 1957
243 Graham J B Biochemical genetics of blood coagulation *Am J Human Genet 8* 63 1956
244 Graham J B and Barrow E M The pathogenesis of hemophilia An experimental analysis of the anticephalin hypothesis in hemophilic dogs *J Exp M 106* 273 1957
245 Graham J B Barrow E M and Hougie C Stuart clotting defect II Genetic aspects of a "new" hemorrhagic state *J Clin Invest 36* 497 1957
246 Graham J B Buckwalter J A Hartley L J and Brinkhous K M Canine hemophilia Observations on course clotting anomaly and the effect of blood transfusions *J Exp M 90* 97 1949
247 Graham J B McLendon W W and Brinkhous K M Mild hemophilia An allelic form of the disease *Am J M Sc 225* 46 1953
248 Graham J B Penick G D and Brinkhous K M Utilization of antihemophilic factor during clotting of canine blood and plasma, *Am J Physiol 164* 710 1951
249 Graham J H Emerson C P and Anglem T J Postoperative hypofibrinogenemia Diffuse intravascular thrombosis after fibrinogen administration *New Eng J Med 257* 101 1957

218 Fowler W M and Gordon J D Multiple myeloma *Am Pract and Digest Treat 1* 449 1950
219 Frick P G Hemophilia like disease following pregnancy with trans placental transfer of an acquired circulating anticoagulant, *Blood 8* 598 1953
220 Frick P G Acquired circulating anticoagulants in systemic "collagen" disease Auto immune thromboplastin deficiency *Blood 10* 691 1955
221 Frick P G Inhibition of conversion of fibrinogen to fibrin by abnormal proteins in multiple myeloma *Am J Clin Path 25* 1263 1955
222 Frick P G Acute hemorrhagic syndrome with hypofibrinogenemia in metastatic cancer *Acta haemat 16* 11 1956
223 Frick P G and Hagen P S Severe coagulation defect without hemorrhagic symptoms caused by a deficiency of the fifth plasma thromboplastin precursor, *J Lab Clin Med 47* 592 1956
224 Frommeyer W B Epstein R D and Taylor F H L Refractoriness in hemophilia to coagulation promoting agents Whole blood and plasma derivatives *Blood 5* 401, 1950
225 Gairdner D The Schonlein Henoch syndrome, *Quart J Med* n s *17* 95 1948
226 Gardner, F H and Diamond L. K. Autoerythrocyte sensitization A form of purpura producing painful bruising following autosensitization to red blood cells in certain women *Blood 10* 675 1955
227 Gardner F H Howell D and Hirsch E O Platelet transfusions utilizing plastic equipment *J Lab Clin Med 43* 196 1954
228 Gardner F H McElfresh A E Harris J W and Diamond L K The effect of adrenocorticotrophic hormone (ACTH) in idiopathic acquired hemolytic anemia as related to the hemolytic mechanisms *J Lab Clin Med 37* 444 1951
229 Gautier P and Guinard Doniol J Un cas de maladie de Lobstein associée à une thrombasthénie héréditaire et familiale de Glanzmann *Bull et Mem Soc Med d'Hôp de Paris 68* 577 1952
230 Gendel B J Young J M and Kraus A P Thrombotic thrombocytopenic purpura *Am J Med 13* 3 1952
231 Gerbode F., Osborn J J Melrose D G Perkins H A Norman A and Baer D M Extracorporeal circulation in intracardiac surgery A comparison between two heart lung machines *Lancet 2* 284 1958
232 Gilon E Ramot B and Sheba C Multiple hemangiomata associated with thrombocytopenia Remarks on the pathogenesis of the thrombocytopenia in this syndrome *Blood 14* 74 1959
233 Gitlin D and Borges W H Studies on the metabolism of fibrinogen in two patients with congenital afibrinogenemia *Blood 8* 679 1953
234 Glanzmann E Hereditare hamorrhagische Thrombasthenie Ein

C V Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura *J Lab & Clin Med* 38 1 1951

267 Harrington W J Sprague C C Minnich V Moore C V Aulvin R C and Dubach R Immunologic mechanisms in idiopathic and neonatal thrombocytopenic purpura *Ann Int Med* 38 433 1953

268 Harrison D F N Babington s disease hereditary haemorrhagic telangiectasia An evaluation of a new method of treatment *Guy s Hosp Rep* 105 246 1956

269 Hartmann F and Langer H Untersuchungen uber den Prothrombin und Ac-globulingehalt des Blutes bei Leberschaden *Deut Arch klin Med* 197 438 1950

270 Hartmann J R and Diamond L K Natural history of 73 patients with hemophilia and related hemorrhagic diseases *Arch Dis Childhood* 90 594 1955

271 Hartmann, R C Hemorrhagic disorder occurring in patients with cyanotic heart disease *Bull Johns Hopkins Hosp* 91 49 1952

272 Hartmann R C Conley C L and Krevans J R The effect of intravenous infusion of thromboplastin on "Heparin Tolerance" *J Clin Invest* 30 948 1951

273 Harvey A M Shulman L E Tumulty P A Conley C L and Schoenrich E H Systemic lupus erythematosus Review of the literature and clinical analysis of 138 cases *Medicine* 33 291 1954

274 Hauser F Über hereditare und symptomatische congenitale Thrombopenie *Ann Paediat Basel* 171 86 1948

275 Hawkins W B and Brinkhous K M Prothrombin deficiency the cause of bleeding in bile fistula dogs *J Exp M* 63 795 1936

276 Hawkins W B and Whipple G M Bile fistulas and related abnormalities bleeding osteoporosis cholelithiasis and duodenal ulcers *J Exp M* 62 599 1935

277 Heal F C and Kent G Purpura fulminans with afibrinogenaemia *Canad M Assn J* 69 367 1953

278 Hellman L M Shettles L B and Eastman N J Vitamin K in obstetrics A review of one year s experience *Am J Obst* 40 844 1940

279 Heni, F and Krauss I Angeborene familiare Gerinnungsstorung durch heparinartigen Hemmkorper *Klin Wschr* 34 747 1956

280 Henry E L Rosenthal, R L and Hoffman I Spontaneous hemorrhages caused by plasma thromboplastin antecedent deficiency Report of a case *J A M A* 162 727 1956

281 Hertzog A J Essential thrombocytopenic purpura Autopsy findings in 36 cases *J Lab & Clin Med* 32 618 1947

282 Hicks N D and Pitney W R A rapid screening test for disorders of thromboplastin generation, *Brit J Haemat* 3 227 1957

250 Gram, H C The blood platelets in influenza with remarks on the technic of counting *Acta med scand* 54 1 1920
251 Greaves J D and Schmidt C L A Nature of the factor concerned in loss of blood coagulability of bile fistula rats *Proc Soc Exp Biol* 37 43 1937
252 Greenberg E On nonclotting component of postpartum blood *Am J Obst* 50 532 1945
253 Greenwalt T J and Triantaphyllopoulos D C Coagulation studies in abruptio placentae complicated by hypofibrinogenemia *Am J Clin Path* 24 1248 1954
254 Grossman B J Heyn R M and Rozenfeld I H Coagulation studies in the newborn infant I Normal infants *Ped* 9 182 1952
254a Grossman L A and Wolff S M Acute thrombocytopenic purpura in infectious mononucleosis *J.A M A* 171 2208 1959
254b Gunz, F W Hemorrhagic thrombocythemia A critical review *Blood* 15 706 1960
255 Habich, H Zur Antigenanalyse der Paraproteine bei Makroglobulinamien *Schweiz med Wschr* 83 1253 1953
256 *Ham T H and Curtis F C Plasma fibrinogen response in man* Influence of the nutritional state induced hyperpyrexia infectious disease and liver damage *Medicine* 17 413 1938
257 Hambrick G Jr Dysproteinemic purpura of the hypergamma globulinemic type Clinical features and differential diagnosis *A M A Arch Derm* 77 23 1958
258 Hanes F M Multiple hereditary hemorrhagic telangiectasia causing hemorrhage (hereditary hemorrhagic telangiectasia) *Bull Johns Hopkins Hosp* 20 63 1909
259 *Hardisty R M "Acquired haemophilia like disease"* Report of a case with studies on the mode of action of the circulating anti coagulant *J Clin Path* 7 26 1954
260 Hardisty R M and Margolis J The role of Hageman factor in the initiation of blood coagulation *Brit J Haemat* 5 203 1959
261 Hardisty R M and Wolff H H Haemorrhagic thrombocythaemia *Brit J Haemat* 1 390 1955
262 Harmon M C Zipursky A. and Lahey M E A study of hemophilia *A M.A J Dis Child* 93 375 1957
263 Harrington W J Therapy of the purpuras *J Chronic Dis* 6 365 1957
264 Harrington W J *The Purpuras* Disease-a Month Chicago Year Book Publishers 1957
✓265 Harrington W J Manheimer R H Desforges J F Minkel H P Crow C B and Stohlman F The bleeding tendency in hepatocellular and obstructive jaundice *Bull New Eng Med. Center* 12 121 1950
266 Harrington, W J Minnich, V Hollingsworth, J W and Moore

Henoch 1 Reproduction expérimentale par un immun sérum 2° test décelant le pouvoir capillaro toxique de l immun sérum et du sérum de malades *Rev franç d'étud Clin et biol* *I* 57 1956
300 Israels M C G Lempert H and Gilbertson E Hemophilia in female *Lancet* *1* 1375 1951
301 Ivy A C Shapiro P F and Melnick P The bleeding tendency in jaundice *Surg Gyn Obst* *60* 781 1935
302 Jackson D P Hartmann R C and Busby T Fibrinogenopenia complicating pregnancy Clinical and laboratory studies *Obst Gyn* *5* 223 1955
303 Jackson D P Hartmann R C and Conley C L Clot retraction as a measure of platelet function II Clinical disorders associated with qualitative platelet defects (Thrombocytopathic purpura) *Bull Johns Hopkins Hosp* *93* 370 1953
304 Jacobs P H Ehler Danlos syndrome Report of a case with onset at age 29 *A M A Arch Derm* *76* 460 1957
305 James T N Monto R W and Rebuck J W Thrombocytopenia and abnormal bleeding in multiple myeloma *Ann Int Med* *39* 1281 1953
306 Jaques L B Bell H J and Cho M H *The Physiology of Heparin in Thrombosis and Embolism Proceedings of the First International Conference on Thrombosis and Embolism* T Koller and W R Merz edit Basel, Benno Schwabe & Co 1955
307 Jaques L B Charles A F and Best C H The administration of heparin *Acta med scand Suppl* *90* 190 1938
308 Jaques L B Fidler E Feldstedt E T and MacDonald A G Silicones and blood coagulation *Canad M Assn J* *55* 26 1946
309 Jaques L B and Waters E T The isolation of crystalline heparin from the blood of dogs in anaphylactic shock *Am J Physiol* *129* 389 1940
310 Jarcho S Diffusely infiltrative carcinoma A hitherto undescribed correlation of several varieties of tumor metastases *Arch Path* *22* 674 1936
311 Jenkins J S Haemorrhagic diathesis due to deficiencies of factor VII *J Clin Path* *7* 29 1954
312 Jim R T S A study of the plasma thrombin time *J Lab & Clin Med* *50* 45 1957
313 Jim R T S and Steinkamp R C Macroglobulinemia and its relationship to other paraproteins *J Lab & Clin Med* *47* 540 1956
314 Jones H W and Tocantins L M Purpura hemorrhagica further notes on the treatment *Tr A Am Physicians* *51* 59 1936
315 Jones T B and Smith H P The blood fibrinogen level in hepatectomized dogs and an outline of a method for the quantitative determination of fibrinogen *Am J Physiol* *94* 144 1930

283 Higgins W H and Higgins W H Jr Primary amyloidosis A clinical and pathological study, *Am J M Sc* 220 610 1950
284 Highstein B and Zeligman, I Nonthrombocytopenic purpura caused by mentholated cigarettes *J A M A* 146 816 1951
285 Hirsch E O and Dameshek W "Idiopathic" thrombocytopenia Review of 89 cases with particular reference to differentiation and treatment of acute (self limited) and chronic types *A M A Arch Int Med* 88 701 1951
286 Hirsch, E O and Gardner, F H The transfusion of human blood platelets with a note on the transfusion of granulocytes *J Lab & Clin Med* 39 556 1952
287 Hjort P Intermediate reactions in the coagulation of blood with tissue thromboplastin *Scand J Clin Lab Invest* 9 Suppl 27, 1 1957
288 Hjort P Rapaport S I and Owren P H Evidence that platelet accelerator (platelet factor 1) is adsorbed plasma proaccelerin *Blood* 10 1139, 1955
289 Hodgson C H Burchell H B Good C A and Claggett O T Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula Survey of a large family *New Eng J Med* 261 625 1959
290 Horder M H Isolierter Faktor V Mangel bedingt durch einen spezifischen Hemmkorper *Acta haemat* 12 1, 1954
291 *Horler A R and Witts L J Hereditary capillary purpura (von Willebrand's Disease) Q J Med n s* 27 173 1958
292 Hougie C Barrow E M and Graham J B Stuart clotting defect. Segregation of hereditary hemorrhagic state from heterogeneous groups heretofore called stable factor" (SPCA, proconvertin, factor VII) deficiency, *J Clin Invest* 36 485 1957
293 Hougie C and Glover H M The hemophilioid states *A M.A. Arch Int Med* 103 239 1959
294 Humble J G The mechanism of petechial hemorrhage formation, *Blood* 4 69 1949
295 Huntley C C and Dees S C Eczema associated with thrombocytopenic purpura and purulent otitis media *Ped* 19 351 1957
296 Hurst A F Hampson A C, Plummer N S and Yates A G Hereditary telangiectasia with haemorrhagic tendency *Guy's Hosp Rep* 82 81 1932
297 Hutt, M S R Richardson J S and Staffurth J S Felty's syndrome A report of 4 cases treated by splenectomy *Q J Med n.s* 20 57, 1951
298 Hyun B H Dawson E A and Custer R P Evaluation of thrombocythemia by the thromboplastin generation test, *Am J Clin Path* 29 539 1958
299 Israel, L Mathé G and Bernard J Sur le syndrome de Schönlein-

332 Kolars C P and Spink W W Thrombopenic purpura as a complication of mumps *J A M A 168* 2213 1958
333 Koller F (moderator) Side-effects and contra indications of anticoagulants *Thrombosis et Diathesis Haemorrhagica 2* 604 1958
334 Koller F Krusi G and Luchsinger G Über eine besondere Form hämorrhagischer Diathese *Schweiz. med Wschr 80* 1101 1950
335 Komrower G M and Watson G H Prognosis in idiopathic thrombocytopenic purpura of childhood *Arch Dis Childhood 29* 502 1954
336 Korn E D Synthesis of heparin by slices of mouse mast cell tumor *J Biol Chem 234* 1321 1959
337 Krevans J R and Jackson D P Hemorrhagic disorder following massive whole blood transfusions *J A M A. 159* 171 1955
338 Krivit, W and Good R A. Aldrich s syndrome (thrombocytopenia eczema and infections in infants) Studies of the defense mechanisms *A M A J Dis Child 93* 74 1957
339 Kugelmass I Cortisone in allergic purpura of children *N Y State J M 51* 2504 1951
340 Kuhlback, B The bleeding tendency in chronic renal failure *Acta med scand. 157* 174 1957
341 Langdell R D *Transfusion Therapy in Hemophilia* in *Hemophilia and Hemophilioid Diseases* K. M Brinkhous edit Chapel Hill U of N Carolina Press 1957
342 Langdell R D Adelson E Furth F W and Crosby W H Dextran and prolonged bleeding time Results of a 60 gram one liter infusion given to 163 normal human subjects *J A M A 166* 346 1958
343 Langdell R D and Hedgpeth E M Jr A study of the role of hemolysis in the hemostatic defect of transfusion reactions *Thromb et Diath Haem 3* 566 1959
344 Langdell R D Wagner R H and Brinkhous K. M Effect of antihemophilic factor on one stage clotting tests *J Lab & Clin Med 41* 637 1953
345 Larrain C and Langdell R D Hemostatic defect of uremia II Investigation of dogs with experimentally produced acute urinary retention *Blood 11* 1067 1956
346 Larrieu M J Syndrome hémorragiques nouvellement identifiés *Rev d'hémat 8* 374 1953
347 Larrieu M J Beaumont J L Caen J Seligmann M and Bernard J Inhibition de la conversion due fibrinogène au cours d un myélome *Rev franç d'Etudes clin et biol 3* 617 1958
348 Larrieu, M J and Soulier J P Deficit en facteur antihemophilique A chez une fille associe a un trouble du saignement, *Rev d'hémat 8* 361 1953

316 Jordan F L J Organization of the "Thrombosis Service" in the Netherlands *Thrombosis et Diathesis Haemorrhagica* 2 527 1958
317 Jordan H H *Hemophilic Arthropathies* Springfield Charles C Thomas 1958
318 Jorpes J E *Heparin in the Treatment of Thrombosis* An account of its chemistry physiology and application in medicine London, Oxford University Press 1946
319 Josephson A M and Lisker, R Demonstration of a circulating anticoagulant in plasma thromboplastin antecedent deficiency *J Clin Invest* 37 148 1958
320 Josse J W and Zacks S I Thymoma and pancytopenia Report of a case and review of the literature *New Eng J Med.* 259 113 1958
321 Jurgens R and Ferlin A. Ueber den sog Prothrombin konsumptions test bei Hamophilie und bei konstitutioneller Thrombopathie *Schweiz med Wschr* 80 1098 1950
322 Jurgens R Lehmann W Wegelius O Eriksson A W and Hiepler E Mitteilung über den Mangel an antihamophilem Globulin (Faktor VIII) bei der Aalandischen Thrombopathie (v Willebrand Jurgens) *Thromb et Diath Haem* 1 257 1957
323 Jurgens R and Trautwein, H Über Fibrinopenie (Fibrinogenopie) beim Erwachsenen nebst Bemerkungen uber die Herkunft des Fibrinogens *Deut Arch klin Med* 169 28 1930
324 Kaplan L and Hartman S W Elastica disease Case of Gronblad Strandberg syndrome with gastrointestinal hemorrhage *A M A Arch Int Med* 94 489 1954
325 Kay E B Zimmerman H A Berne R M Hirose Y Jones R D and Cross F S Certain clinical aspects of the use of a pump oxygenator *J A M A* 162 639 1956
326 Keil H Relation between "systemic" lupus erythematosus and a peculiar form of thrombocytopenic purpura, *Brit J Derm* 49 221 1937
327 Kellaway C H Snake venoms I Their constitution and therapeutic applications *Bull Johns Hopkins Hosp* 60 1 1937
328 Kelly E H Purpura fulminans following measles *Brit J Child Dis* 19 86 1922
329 King, H and Shumacker H B Jr Splenic studies I Susceptibility to infection after splenectomy performed in infancy *Ann Surg* 136 239 1952
330 Kingsley C S Familial factor V deficiency, pattern of heredity *Q J Med n.s* 23 323 1954
331 Koch H J Jr Escher G C and Lewis J S Hormonal management of hereditary hemorrhagic telangiectasia *J A M A* 149 1376 1952

365 Lewis J H Ferguson J H Fresh, J W and Zucker M B Primary hemorrhagic diseases *J Lab & Clin Med.* *49* 211 1957
366 Lewis J H Zucker M B and Ferguson J H Bleeding tendency in uremia *Blood 11* 1073 1956
367 Lewisohn R The citrate method of blood transfusion in retrospect, *Acta haemat* *20* 215 1958
368 Limarzi L R and Schleicher E M The reaction of peripheral blood and bone marrow in chronic hemorrhage and in essential thrombopenic purpura *J.A M.A* *114* 12 1940
369 Lasker R Josephson, A. M Werbin, G Shapiro C M and Rozeng vaig S The correction of a hemorrhagic diathesis in preparation for surgery The correction of plasma thromboplastin antecedent deficiency *A M A Arch Int Med* *100* 474 1957
370 Little J M Wallace S L Bobb J R R and Crothers W C Perirenal hemorrhage in ureter ligated dogs receiving phthalylsulfa thiazole *Proc Soc Exper Biol & Med* *66* 338 1947
371 Little J R Purpura fulminans treated successfully with anticoagula tion *J.A M.A* *169* 36 1959
372. Lohmuller H W Thrombotic thrombocytopenic purpura Report of 2 cases *A M.A Arch Int Med* *100* 267 1957
373 Lombardo L J Jr Fibrinolysin in urologic patients *J.A M.A* *169* 1718 1959
374 Long, L A Letendre P and Colpron G Hypoproconvertinémie congénitale *Acta haemat* *13* 242 1955
375 Lorand L and Jacobsen A Studies on the polymerization of fibrin The role of the globulin fibrin stabilizing factor *J Biol Chem* *230* 421 1958
376 Lorand L and Middlebrook, W R Studies on fibrino-peptide *Biochem et biophys acta* 9 581 1952
377 Lord J W Jr and Andrus W deW Differentiation of intra hepatic and extrahepatic jaundice Response of the plasma prothrombin to intramuscular injection of menadione (2 methyl 1 4 naphthoquinone) as a diagnostic aid *A M A Arch Int Med* *49* 199 1941
378 Loria P R Kennedy C B Freeman J A and Henington V M Pseudoxanthoma Elasticum (Gronblad Strandberg syndrome) A clinical, light and electron microscopic study *A.M.A Arch Derm* *76* 609 1957
379 Lozner E L Differential diagnosis pathogenesis and treatment of the thrombocytopenic purpuras *Am J Med* *14* 459 1953
381 MacAusland W R Jr and Gartland J J Treatment of acute hemophilic hemarthrosis *New Eng J Med* *247* 755 1952
381a. McCain K F Chernoff A T and Graham J B *Establishment of the Inheritance of Hageman Defect as an Autosomal Recessive Trait in Hemophilia and Other Hemorrhagic States* Brinkhous

349 Lasch H G and Roka L Zur Prothrombinbildung in der Leber *Ztschr physiol chem 294* 30 1953
350 Laurell A B and Nilsson I M Hypergammaglobulinemia, circulating anticoagulant and biologic false positive Wassermann reaction A study in two cases *J Lab & Clin Med 49* 694 1957
351 Lauridsen J Belko J S and Warren R Alterations in circulating platelets following administration of adrenocorticotropic hormone *Proc Soc Exp Biol* 79 709 1952
352 Lawrence J S and Craddock C G Jr Hemophilia The mechanism of development and action of an anticoagulant found in two cases *Science 106* 473 1947
353 Lawrence J S and Johnson J B The presence of a circulating anti coagulant in a male member of a hemophiliac family *Tr Am Clin Climat Assn 57* 223 1941
354 Lawson H A Congenital afibrinogenemia *New Eng J Med 248* 552 1953
355 Learmonth J The surgery of the spleen *Brit M J 2* 67 1951
356 Leavitt L M and Burbank B Glomerulonephritis as a complication of the Schonlein Henoch syndrome *New Eng J Med 248* 530 1953
357 Lee S L and Sanders M A disorder of blood coagulation in systemic lupus erythematosus *J Clin Invest 34* 1814 1955
358 Leeksma C H W and Cohen J A Determination of the life span of human blood platelets using labelled diisopropyl fluorophosphonate *J Clin Invest* 35 964 1956
359 Leese W L B Prolonged treatment of the Schonlein Henoch syndrome with corticotrophin *Lancet 2* 851 1955
360 Leonhardt T Familial hypergammaglobulinaemia and systemic lupus erythematosus *Lancet 2* 1200 1957
361 Lerner A B and Watson C J Studies of cryoglobulins I Unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin) *Am J M Sc 214* 410 1947
362 LeSourd L and Pagniez P L irrétractilité du caillot et sa production expérimentale par action directe sur les hématoblastes *C rend Soc Biol 61* 562 1906
362a Lewis J H Personal communication
363 Lewis J H Burchenal, J H Ellison R R Ferguson J H Palmer J H Murphy M L and Zucker M B Studies of hemostatic mechanisms in leukemia and thrombocytopenia *Am J Clin Path 28* 433 1957
364 Lewis J H Ferguson J H and Arends T Hemorrhagic disease with circulating inhibitors of blood clotting Anti AHF and anti PTC in 8 cases *Blood 11* 846 1956

in paroxysmal nocturnal haemoglobinuria *Brit J haemat* *4* 404 1958

399 McKusick, V *Heritable Disorders of Connective Tissue* Second Edition St Louis C V Mosby Co 1960

400 McLean S Kreidel K and Caffey J Hemorrhagic thrombocytopenia in childhood A clinical study of 21 cases *J.A.M.A* *98* 387 1932

401 MacMillan R L. and Brown K. W G Heparin and thromboplastin *J Lab & Clin Med* *44* 378 1954

402 Madison F W and Quick A J A hemophilia like disease in the female with a note on the clotting time of the recalcified plasma, *Am J M Sc* *209* 443 1945

403 Mallarmé J and Auzery P Distinction nosographique (clinique et hématologique) des thrombocythémies *Le Sang* *28* 210 1957

404 Mann F D Reactivity of hemophilic plasma to platelet thromboplastin *J Lab & Clin Med* *48* 51 1956

405 Mann F D Shonyo E S and Mann F C Effect of removal of the liver on blood coagulation *Am J Physiol* *164* 111 1951

406 Marcus A J and Spaet T H Platelet phosphatides Their separation identification and clotting activity *J Clin. Invest* *37* 1836 1958

407 Marder M Weiner M Shulman P and Shapiro S Afibrinogenemia occurring in a case of malignancy of the prostate with bone metastases *New York J Med* *49* 1197 1949

408 Margolius A Jr Jackson D P Ratnoff O D and Conley C L Circulating anticoagulants a study of 40 cases and a review of the literature To be published

409 Margolius A Jr and Ratnoff O D Observations on hereditary nature of Hageman trait *Blood* *11* 565 1956

409a Margolius A Jr and Ratnoff O D A laboratory study of the carrier state in classic hemophilia *J Clin Invest* *35* 1316 1956

410 Margolius A. Jr and Ratnoff O D Unpublished observations

411 Margolis J Glass surface and blood coagulation *Nature* *178* 805 1956

412 Margolis J Initiation of blood coagulation by glass and related surfaces *J Physiol* *137* 95 1957

413 Margolis J Activation of plasma by contact with glass Evidence for a common reaction which releases plasma kinin and initiates coagulation *J Physiol* *144* 1 1958

414 Margolis J Activation of a permeability factor in plasma by contact with glass *Nature* *181* 635 1958

415 Margulis R R Luzadre J H and Hodgkinson C P Fibrinolysis in labor and delivery *Obst & Gynec* *3* 487 1954

416 Marley E Non thrombocytopenic purpura after administration of chlorpromazine hydrochloride *Brit M J* *2* 1126 1955

K M and de Nicola P edit Chapel Hill U of N Carolina Press 1959
382 McCormick H M and Young I I Effect of aminophylline on plasma prothrombin and ac globulin in dogs *Proc Soc Exper Biol & Med 70* 501 1949
383 McCreary J and Wurzel H Poisonous snake bites Report of a case *J A M A 170* 268 1959
384 McElfresh A Personal Communication
385 McElfresh A E Sharpsteen J R and Akabane T The generation of thromboplastin and levels of plasma thromboplastin component in the blood of infants *Ped 17* 871 1956
386 MacFarlane J C W and Simpkiss M J The investigation of a large family with von Willebrand s disease *Arch Dis Childhood* 29 483 1954
387 Macfarlane R G A simple method for measuring clot retraction, *Lancet 1* 1199 1939
388 Macfarlane R G Critical review Mechanism of haemostasis *Q J Med n s 10* 1 1941
389 Macfarlane R G *The Reactions of the Blood to Injury Blood Coagulation and Hemostasis Changes in the Blood Cells and the Activation of Fibrinolysis* in *General Pathology* H Florey edit Philadelphia W B Saunders Co 1958
390 Macfarlane R G and Biggs R Observations on fibrinolysis Spontaneous activity associated with surgical operations trauma etc *Lancet 2* 862 1946
391 Macfarlane R G and Biggs R The diagnosis and treatment of hemophilia and related conditions *Medical Research Council Memorandum* No 32 London H M Stationery office 1955
392 McGovern J J Platelet transfusions in pediatrics *New Eng J Med 256* 922 1957
393 McGovern J J and Steinberg A G Anti hemophilic factor deficiency in a female *J Lab & Clin Med 51* 386 1958
394 McKay D G Hardaway R M Wahle G H Edelstein R and Tartock D E Alterations in blood coagulation mechanisms after incompatible blood transfusion *Am J Surg 89* 583 1955
395 McKay D G Jewett J F and Reid D E Endotoxin shock and the generalized Shwartzman reaction in pregnancy *Am J Obst & Gyn 78* 546 1959
396 McKay D G Mansell H and Hertig A T Carcinoma of the body of the pancreas with fibrin thrombosis and fibrinogenopenia *Cancer* 6 862 1953
397 MacKay I R Eriksen N Motulsky A G and Volwiler W Cryo- and macroglobulinemia Electrophoretic ultracentrifugal and clinical studies *Am J Med 20* 564 1956
398 McKellar M and Dacie J V *Thromboplastic activity of the plasma*

434. Middlebrook J E Hypofibrinogenemia without fibrinolysis associated with a lymphoma and controlled after treatment with cortisone and nitrogen mustard *Ann. Int Med* *47* 1242 1957

435 Miller L. and Bale W F Synthesis of all plasma protein fractions except gamma globulins by the liver The use of zone electrophoresis and lysine-ε C^{14} to define the plasma proteins synthesized by the isolated perfused liver *J Exper Med* *99* 125 1954

436 Miller L L Bly C G Watson M L and Bale W F The dominant role of the liver in plasma protein synthesis A direct study of the isolated perfused rat liver with the aid of lysine-ε C' *J Exper Med.* *94* 431 1951

437 Mills C A The action of tissue extracts in the coagulation of blood, *J Biol Chem* *46* 167 1921

438 Mills S D and Winkelmann, R K Eczema thrombocytopenic purpura and recurring infections *A M.A Arch Derm* 79 466 1959

439 Milstone J On the evolution of blood clotting theory *Medicine* *31* 411 1952

440 Minot, G R Purpura hemorrhagica with lymphocytosis an acute type and an intermittent menstrual type *Tr A Am Physicians* *51* 69 1936

440a Mirsky I A Perisutti, G and Davis M C The destruction of glucagon adrenocorticotrophin and somatotropin by human blood plasma, *J Clin Invest* 38 14 1959

441 Mohler D N Smith D E and Leavell B S Exogenous hemochromatosis occurring in aplastic anemia An autopsy study on 14 patients *Clin Res Proc* *6* 116 1958

442 Moloney W C Egan W J and Gorman A J Acquired afibrinogenemia in pregnancy *New Eng J Med* *240* 596 1949

443 Moor Jankowski, J K Huser H J Rosin, S Truog G Schneeberger M and Geiger M *Hemophilia B-Genetics Hematology and Clinical Aspects* Basel, S Karger 1958

444 Moore T and Sharman I M Danger of Vitamin K analogues to newborn *Lancet* *I* 819 1955

445 Morawitz P *The Chemistry of Blood Coagulation [Ergebn der Physiol* *4* 307 1905] Robert C Hartmann and Paul F Guenther transl Springfield Charles C Thomas 1958

446 Morton, J I and Deutsch, H F Human serum macroglobulins and dissociation units II Immunochemical properties *J Biol Chem* *231* 1119 1958

447 Moschcowitz E An acute pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries *A M A Arch Int Med* *36* 89 1925

448 Moyer J H and Ackerman A. J Hereditary hemorrhagic telangiectases associated with pulmonary arteriovenous fistula in two members of a family *Ann Int Med* 29 775 1948

417 Marriott H J L Primary systemic amyloidosis *Ann Int Med* 38 620 1953
418 Mars G Gianotti F and Coronelli M Considérations sur l'étiologie et la pathogenie du purpura sénile de Bateman avec en particular son rapport avec la vitamine E *Presse med* 65 2146 1957
419 Marshall R J and McCaughey W T E Hypothermic myxoedema coma with muscle damage and acute renal tubular necrosis *Lancet* 2 754 1956
420 Martin N H and Close H G Macroglobulinaemia *Lancet* 2 8 1957
421 Martius C and Nitz Litzow D Über den Werkungsmechanismus des Dicumarol und Verwandter Verbindungen *Biochim et biophys acta* 12 134 1953
422 Mason M F and Evers R Observations on the proteolytic activity of the sera of dogs with experimental uremia *J Biol Chem* 119 735 1937
423 Masure R Pseudo hemophilie feminine acquise due a la présence d un inhibiteur du facteur antihémophilique A *Rev belge de Path et de Méd Exper* 24 23 1955
424 Matter M Newcomb T F Melly A and Finch C A Vascular hemophilia The association of a vascular defect with a deficiency of antihemophilic globulin *Am J M Sc* 232 421 1956
425 Mattison W E Jr Experimental thrombocytopenia and platelet agglutination *Bull Johns Hopkins Hosp* 104 63 1959
426 Meacham G C Orbison J L Heinle R W Steele H J and Schaefer J A Thrombotic thrombocytopenic purpura A disseminated disease of arterioles *Blood* 6 706 1951
426a Medal L S and Lisker R Circulating anticoagulants in disseminated lupus erythematosus *Brit J Haemat* 5 284 1959
427 Medearis D N Jr Cytomegalic inclusion disease *Ped* 19 467 1957
428 Merskey C Haemophilia associated with normal coagulation time *Brit M J* 1 906 1951
429 Merskey C Occurrence of haemophilia in human female *Quart J Med n s* 20 299 1951
430 Merskey C Bantu haematology and coagulation *The Leech* 28 45 1958
431 Merskey C and Hansen J D L Blood coagulation defects in kwashiorkor and infantile gastroenteritis *Brit J Haemat* 3 39 1957
432 Merskey C and Macfarlane R G Female carrier of haemophilia clinical and laboratory study *Lancet* 1 487 1951
433 Michael S R Vural I L Bassen F A and Schaeffer L The hematologic aspects of disseminated (systemic) lupus erythematosus *Blood* 6 1059 1951

autosomal hemorrhagic diathesis with antihemophilic globulin (AHG) deficiency and prolonged bleeding time *Acta med scand* *159* 35 1957

466 Nilsson I M and Wenckert A Demonstration of a heparin like anticoagulant in normal blood *Acta med scand* *150* *Suppl 297* 1 1954

467 Obata I On the nature of eclampsia *J Immunol* *4* 111 1919

468 O'Brien J L and Sibley W A Neurologic manifestations of thrombotic thrombocytopenic purpura *Neurology* *8* 55 1958

469 Olwin J H Differentiation of surgical jaundice from severe damage of liver (subacute yellow atrophy) clinically simulating it *Arch Surg* *43* 633 1941

470 Orbison J L Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms *Am J Path* *28* 129 1952

471 Osgood E E Koler R D and Hughes M F Differential diagnosis and treatment of hemorrhagic diseases *A M.A. Arch Int Med* *94* 956 1954

472 Osler W On a familial form of recurring epistaxis associated with multiple telangiectases of the skin and mucous membrane *Bull Johns Hopkins Hosp* *12* 333 1901

473 Osler W On multiple hereditary telangiectases with recurring haemorrhages *Quart J M* *1* 53 1907

474 Osler W The visceral lesions of purpura and allied conditions *Brit M J* *1* 517 1914

475 Owren P A Coagulation of blood Investigation of new clotting factor *Acta med scand Suppl 194* 1 1947

476 Owren P A Prothrombin and accessory factors Clinical significance *Am J Med* *14* 201 1953

476a. Ozer F L Truax W E Miesch, D C and Levin, W C Primary hemorrhagic thrombocythemia *Am J Med* *28* 807 1960

477 Page E W Fulton L D and Glendening M B Cause of blood coagulation defect following abruptio placentae *Am J Obst & Gynec* *61* 1116 1951

478 Patek A J Jr and Stetson R P Hemophilia abnormal coagulation of blood and its relation to blood platelets *J Clin Invest* *15* 531 1936

479 Patek A J Jr and Taylor F H L Hemophilia some properties of substance obtained from normal human plasma effective in accelerating coagulation of hemophilic blood *J Clin Invest* *16* 113 1937

480 Pavlovsky A Contribution to pathogenesis of hemophilia *Blood* 2 185 1947

480a Pavlovsky A and de Pavlovsky M C *Female Hemophilia in Hemophilia and Other Hemorrhagic States* Brinkhous K M and de Nicola P edit Chapel Hill U of N Carolina Press 1959

449 Mueller J F Ratnoff O D and Heinle R W Observations on the characteristics of an unusual circulating anticoagulant, *J Lab & Clin Med 38* 254 1957
450 Muirhead E E Incompatible blood transfusions with emphasis on renal failure *Surg Gynec & Obst 92* 734 1951
451 Muirhead E E Crass G and Hill J M Diffuse platelet thromboses with thrombocytopenia and hemolytic anemia (thrombotic thrombocytopenic purpura) *Am J Clin Path 18* 523 1948
452 Muirhead E E Vanatta J and Grollman A Hypertensive cardiovascular disease An experimental study of tissue changes in bilaterally nephrectomized dogs *Arch Path 48* 234 1948
453 Muldoon, J P, Berg A M and Kinnaird D W Surgical implications of non thrombocytopenic purpura *Ann Surg 142* 817 1955
454 Munro F L and Jones H W The detrimental effect of frequent transfusions in the treatment of patients with hemophilia *Am J Med Sc 206* 710 1943
455 Munro F L and Munro M P Electrophoretic isolation of a circulating anticoagulant *J Clin Invest 25* 814 1946
456 *Nathan D J and Snapper I Simultaneous placental transfer of factors* responsible for L E cell formation and thrombocytopenia *Am J Med 25* 647 1958
457 Nelken D Gilboa N and Gurevitch J Osmotic fragility of human blood platelets III Normal and pathological values *J Lab & Clin Med 56* 120 1960
458 Nelson R M Eder W P Eddy F D Karlson K E and Dennis C Production of a hemorrhagic state by the infusion of hemolyzed blood *Proc Soc Exper Biol & Med 73* 208 1950
459 Neustadt D H Corticosteroid therapy in rheumatoid arthritis Comparative study of effects of prednisone and prednisolone methyl prednisolone triamcinolone and dexamethasone *J A M A. 170* 1253 1959
460 Newberry W Margolius A Jr and Ratnoff O D Unpublished observations
461 Newcomb T Matter M Conroy, L DeMarsh Q B and Finch, C A A congenital hemorrhagic diathesis of the prothrombin complex *Am J Med 20* 798 1956
462 Newton W A Jr and Zuelzer W W Idiopathic thrombocytopenic purpura in childhood *New Eng J Med 245* 879 1951
463 Nilsson I M Bergman S Reitalu J and Waldenstrom J Hemophilia A in a girl with male sex-chromatin pattern *Lancet 2* 264 1959
464 Nilsson I M Blomback M Jorpes E Blomback, B and Johansson S A V Willebrand s disease and its correction with human plasma fraction I 0 *Acta med scand 159* 179 1957
465 Nilsson I M Blomback M and von Francken I On an inherited

autosomal hemorrhagic diathesis with antihemophilic globulin (AHG) deficiency and prolonged bleeding time *Acta med scand* *159* 35 1957
466 Nilsson I M and Wenckert A. Demonstration of a heparin like anticoagulant in normal blood *Acta med scand* *150* *Suppl* *297* 1 1954
467 Obata I On the nature of eclampsia, *J Immunol* *4* 111 1919
468 O'Brien J L. and Sibley W A Neurologic manifestations of thrombotic thrombocytopenic purpura *Neurology* *8* 55 1958
469 Olwin, J H Differentiation of surgical jaundice from severe damage of liver (subacute yellow atrophy) clinically simulating it, *Arch Surg* *43* 633 1941
470 Orbison J L Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms *Am J Path* *28* 129 1952
471 Osgood E E Koler R D and Hughes M E Differential diagnosis and treatment of hemorrhagic diseases *A.M.A. Arch Int Med* *94* 956 1954
472 Osler W On a familial form of recurring epistaxis associated with multiple telangiectases of the skin and mucous membrane *Bull Johns Hopkins Hosp* *12* 333 1901
473 Osler W On multiple hereditary telangiectases with recurring haemorrhages *Quart J M* *1* 53 1907
474 Osler W The visceral lesions of purpura and allied conditions *Brit M J* *1* 517 1914
475 Owren P A. Coagulation of blood Investigation of new clotting factor *Acta med scand Suppl* *194* 1 1947
476 Owren P A Prothrombin and accessory factors Clinical significance *Am J Med* *14* 201 1953
476a. Ozer F L Truax W E Miesch D C and Levin, W C Primary hemorrhagic thrombocythemia *Am J Med* *28* 807 1960
477 Page E W Fulton L D and Glendening M B Cause of blood coagulation defect following abruptio placentae *Am J Obst & Gynec* *61* 1116 1951
478 Patek, A J., Jr and Stetson, R P Hemophilia abnormal coagulation of blood and its relation to blood platelets *J Clin Invest* *15* 531 1936
479 Patek, A J Jr and Taylor F H L Hemophilia some properties of substance obtained from normal human plasma effective in accelerating coagulation of hemophilic blood *J Clin Invest* *16* 113 1937
480 Pavlovsky A Contribution to pathogenesis of hemophilia *Blood* *2* 185 1947
480a Pavlovsky A and de Pavlovsky M C *Female Hemophilia in Hemophilia and Other Hemorrhagic States* Brinkhous K M and de Nicola P edit Chapel Hill, U of N Carolina Press 1959

449 Mueller J F, Ratnoff O D and Heinle R. W Observations on the characteristics of an unusual circulating anticoagulant *J Lab & Clin Med 38* 254 1957
450 Muirhead E F Incompatible blood transfusions with emphasis on renal failure *Surg Gynec & Obst 92* 734 1951
451 Muirhead E E Crass G and Hill J M Diffuse platelet thromboses with thrombocytopenia and hemolytic anemia (thrombotic thrombocytopenic purpura) *Am J Clin Path 18* 523 1948
452 Muirhead E E, Vanatta J and Grollman A Hypertensive cardiovascular disease An experimental study of tissue changes in bilaterally nephrectomized dogs *Arch Path 48* 234 1948
453 Muldoon J P Berg A M and Kinnaird D W Surgical implications of non thrombocytopenic purpura *Ann Surg 142* 817 1955
454 Munro F L and Jones H W The detrimental effect of frequent transfusions in the treatment of patients with hemophilia *Am J Med Sc 206* 710 1943
455 Munro F L and Munro M P Electrophoretic isolation of a circulating anticoagulant *J Clin Invest 25* 814 1946
456 Nathan D J and Snapper I Simultaneous placental transfer of factors responsible for L-E cell formation and thrombocytopenia *Am J Med 25* 647 1958
457 Nelken D Gilboa N and Gurevitch J Osmotic fragility of human blood platelets III Normal and pathological values *J Lab & Clin Med 56* 120 1960
458 Nelson R M Eder W P Eddy F D Karlson K E and Dennis C Production of a hemorrhagic state by the infusion of hemolyzed blood *Proc Soc Exper Biol & Med 73* 208 1950
459 Neustadt D H Corticosteroid therapy in rheumatoid arthritis Comparative study of effects of prednisone and prednisolone methyl prednisolone triamcinolone and dexamethasone *J.A M A 170* 1253 1959
460 Newberry W Margolius A Jr and Ratnoff O D Unpublished observations
461 Newcomb T Matter M Conroy L DeMarsh Q B and Finch C A A congenital hemorrhagic diathesis of the prothrombin complex *Am J Med 20* 798 1956
462 Newton W A Jr and Zuelzer W W Idiopathic thrombocytopenic purpura in childhood *New Eng J Med 245* 879 1951
463 Nilsson I M Bergman S Reitalu J and Waldenstrom J Hemophilia A in a girl with male sex chromatin pattern *Lancet 2* 264 1959
464 Nilsson I M Blomback M Jorpes E Blomback, B and Johansson S A V Willebrand s disease and its correction with human plasma fraction 1 0 *Acta med scand 159* 179 1957
465 Nilsson I M Blomback M and von Francken I On an inherited

autosomal hemorrhagic diathesis with antihemophilic globulin (AHG) deficiency and prolonged bleeding time *Acta med scand.* *159* 35 1957
466 Nilsson I M and Wenckert, A. Demonstration of a heparin like anticoagulant in normal blood *Acta med scand 150 Suppl 297* 1 1954
467 Obata, I On the nature of eclampsia *J Immunol 4* 111 1919
468 O'Brien, J L. and Sibley W A. Neurologic manifestations of thrombotic thrombocytopenic purpura *Neurology 8* 55 1958
469 Olwin J H Differentiation of surgical jaundice from severe damage of liver (subacute yellow atrophy) clinically simulating it, *Arch. Surg 43* 633 1941
470 Orbison J L. Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms *Am J Path 28* 129 1952
471 Osgood E. E Koler R D and Hughes M E. Differential diagnosis and treatment of hemorrhagic diseases *A.M.A. Arch Int Med 94* 956 1954
472 Osler W On a familial form of recurring epistaxis associated with multiple telangiectases of the skin and mucous membrane *Bull. Johns Hopkins Hosp 12* 333 1901
473 Osler W On multiple hereditary telangiectases with recurring haemorrhages *Quart J M 1* 53 1907
474 Osler W The visceral lesions of purpura and allied conditions *Brit M J 1* 517 1914
475 Owren P A. Coagulation of blood Investigation of new clotting factor *Acta med scand. Suppl 194* 1 1947
476 Owren P A. Prothrombin and accessory factors Clinical significance *Am J Med. 14* 201 1953
476a. Ozer F L. Truax, W E Miesch, D C and Levin W C Primary hemorrhagic thrombocythemia *Am J Med 28* 807 1960
477 Page E W Fulton, L D and Glendening M B Cause of blood coagulation defect following abruptio placentae *Am J Obst & Gynec 61* 1116 1951
478 Patek, A J Jr and Stetson R P Hemophilia abnormal coagulation of blood and its relation to blood platelets *J Clin Invest 15* 531 1936
479 Patek, A. J Jr and Taylor F H L Hemophilia some properties of substance obtained from normal human plasma effective in accelerating coagulation of hemophilic blood *J Clin Invest 16* 113 1937
480 Pavlovsky A. Contribution to pathogenesis of hemophilia, *Blood 2* 185 1947
480a Pavlovsky A and de Pavlovsky M C *Female Hemophilia, in Hemophilia and Other Hemorrhagic States* Brinkhous K. M and de Nicola, P edit. Chapel Hill, U of N Carolina Press 1959

481 Penick G D Averette H E Jr Peters R M and Brinkhous K The hemorrhagic syndrome complicating extracorporeal shunting of blood An experimental study of its pathogenesis *Thromb et Diath Haem 2* 218 1958
482 Penick G D Wagner R H Roberts H P and Brinkhous K M Inactivation of plasma antihemophilic factor (AHF) *Fed Proc 14* 415 1955
483 Pepper H Liebowitz D and Lindsay S Cyclic thrombocytopenic purpura related to the menstrual cycle Report of a case with review of the literature *A M A Arch Path 61* 1 1956
484 Perkins H A Osborn J J and Gerbode F The management of abnormal bleeding following extracorporeal circulation *Ann Int Med 51* 658 1959
485 Perlman E C Purpuric and cerebral manifestations following measles Report of two cases *Arch Pediat 51* 596 1934
486 Perugini S and Soldati M Cytochemical studies of the megakaryocytes and platelets in pathological conditions *Schweiz med Wchn 37* 1437 1956
487 Petermann M L and Braunsteiner H A cryoglobulin of high sedimentation rate (Macroglobulin) from human serum *Arch Bioch Biophys 53* 491 1954
488 Peters, G A Allergic purpura with special references to hypersensitiveness to cold *Proc Staff Meet Mayo Clin 16* 631 1941
489 Peters R A Vitamin C requirement of human adults Experimental study of Vitamin C deprivation in man A preliminary report by the Vitamin C subcommittee of the accessory food factors committee Medical Research Council *Lancet 1* 853 1948
490 Peterson O H and Larson P Thrombocytopenic purpura in pregnancy collective review *Obst & Gynec 4* 454 1954
491 Peyman M A The significance of haemorrhage during the treatment of patients with the coumarin anticoagulants *Acta med scand Suppl 339* 1 1958
492 Philpott, M G The Schonlein Henoch syndrome in childhood with particular reference to the occurrence of nephritis *Arch Dis Childhood 27* 480 1952
493 Philpott, M G and Briggs J N Treatment of the Schonlein Henoch syndrome with adrenocorticotrophic hormone (ACTH) and cortisone *Arch Dis Childhood 28* 57 1953
494 Pifer P W Block M A and Hodgkinson C P Thrombocytopenia and hemorrhage in hemolytic blood transfusion reactions *Surg Gynec & Obst 103* 129 1956
495 Pillemer L Ratnoff O D Blum L and Lepow I H The inactivation of complement and its components by plasmin *J Exper Med 97* 573 1953
496 Pinniger J L and Prunty F T G Some observations on blood

clotting mechanisms role of fibrinogen and platelets with reference to a case of congenital afibrinogenaemia, *Brit J Exper Path* 27 200 1946
497 Pisciotta A. V and Schulz, E J Fibrinolytic purpura in acute leukemia *Am J Med 19* 824 1955
498 Pitney W R. and Arnold S J Antihaemophilic factor in families of haemorrhagic patients *Brit J Haemat* 5 184 1959
499 Pohle F J The blood platelet count in relation to the menstrual cycle in normal women, *Am J Med Sc 197* 40 1939
500 Poinsard P J *Psychiatric Aspects of Hemophilia*, in *Hemophilia & Hemiphilioid Diseases* K M Brinkhous Edit., Chapel Hill U of N Carolina Press 1957
501 Pool J and Robinson J *In vitro* synthesis of coagulation factors by rat liver slices *Am J Physiol 196* 423 1959
502 Powell, G M Clinical manifestations of epidemic hemorrhagic fever *J.A.M.A. 151* 1261 1953
503 Posner A C Purpura hemorrhagica complicating the puerperium, *Am. J Obst & Gynec 34* 155 1937
504 Pritchard J A Hemostatic defects in pregnancy *Am J Obst & Gynec 72* 946 1956
505 Pritchard J A Abruptio placentae and hypofibrinogenemia *Am J Obst & Gynec 76* 347 1958
506 Pritchard J A. and Ratnoff O D Studies of fibrinogen and other hemostatic factors in women with intrauterine death and delayed delivery *Surg Gynec & Obst 101* 467 1955
507 Pritchard J A. Ratnoff O D and Weisman, R Jr Hemostatic defects and increased red cell destruction in preeclampsia and eclampsia *Obst & Gynec 4* 159 1954
508 Pritchard J A Weisman R Jr Ratnoff O D and Vosburgh G J Intravascular hemolysis thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy *New Eng J Med. 250* 89 1954
509 Pritchard J A. and Wright M R Pathogenesis of hypofibrinogenemia in placental abruption *New Eng J Med 261* 218 1959
510 Prout, G R. Siegel, M Cliffton, E E and Whitmore W F Jr Hemorrhagic diathesis in patients with carcinoma of prostate *J.A.M.A 160* 840 1956
511 Quick A J Coagulation defect in sweet clover disease and in hemorrhagic chick disease of dietary origin *Am J Physiol 118* 260 1937
512 Quick, A J The nature of the bleeding in jaundice *J.A.M.A 110* 1658 1938
513 Quick, A J *The Hemorrhagic Diseases and the Physiology of Hemostasis* Springfield, Charles C Thomas 1942

514 Quick A J The anticoagulants effective *in vivo* with special reference to heparin and dicumarol, *Physiol Rev* 24 297 1944
515 Quick A J Studies on enigma of hemostatic dysfunction of hemophilia *Am J Med Sc* 214 272 1947
516 Quick A J Management of hemophilia in general practice *J A M A* 145 4 1951
517 Quick A J *Hemorrhagic Diseases* Philadelphia Lea & Febiger 1957
518 Quick A J and Favre Gilly J E The prothrombin consumption test its clinical and theoretic implications *Blood* 4 1281 1949
519 Quick A J and Grossman A M The nature of the hemorrhagic disease of the newborn Delayed restoration of the prothrombin level *Am J Med Sc* 199 1 1940
520 Quick A J and Hussey C V *Hemophilia Clinical* and laboratory observations relative to diagnosis and inheritance *Am J Med Sc* 223 401 1952
521 Quick A J and Hussey C V Hemophilia B (PTC deficiency or Christmas disease) *A M A Arch Int Med* 103 762 1959
522 Quick A J Pisciotta A V and Hussey C V Congenital hypoprothrombinemic states *A M A Arch Int Med* 95 2 1955
523 Quick A J Stanley Brown M and Bancroft F W A study of the coagulation defect in hemophilia and in jaundice *Am J Med Sc* 190 501 1935
524 Rabinovich S I The long term results of splenectomy in Werlhof's Disease *Problems of Hematology and Blood Transfusions* 2 100 1957
524a Rabinowitz, Y and Dameshek, W *Systemic* lupus erythematosus after "idiopathic" thrombocytopenic purpura A review A study of systemic lupus erythematosus occurring after 78 splenectomies for "idiopathic" thrombocytopenic purpura with a review of the pertinent literature *Ann Int Med* 52 1 1960
525 Ralli E P and Sherry S Adult scurvy and the metabolism of Vitamin C *Medicine* 20 251 1942
526 Ramot, B Angelopoulos B and Singer K *Plasma thromboplastin* antecedent deficiency *A M A Arch Int Med* 95 705 1955
527 Rapaport S I and Chapman C C Coexistent hypercoagulability and acute hypofibrinogenemia in a patient with prostatic carcinoma, *Am J Med* 27 144 1959
528 Rath C E Maillard J A and Schreiner G E Bleeding tendency in uremia *New Eng J Med* 257 808 1957
529 Ratnoff O D Studies on a proteolytic enzyme in human plasma IV The rate of lysis of plasma clots in normal and diseased individuals with particular reference to hepatic disease *Bull Johns Hopkins Hosp* 84 29 1949

530 Ratnoff O D Studies on a proteolytic enzyme in human plasma VII A fatal hemorrhagic state associated with excessive plasma proteolytic activity in a patient undergoing surgery for carcinoma of the head of the pancreas *J Clin Invest 31* 521 1952
531 Ratnoff O D Delayed blood coagulation in multiple myeloma *J Clin Invest* 32 596 1953
✓ 532 Ratnoff O D Accelerating property of plasma for coagulation of fibrinogen by thrombin *J Clin Invest 33* 1175 1954
✓ 533 Ratnoff O D *The Liver Three Aspects of Hepatic Failure Cholemia Ascites and Hemorrhagic Phenomena,* in *Analytic Pathology Treatises in the Perspective of Biology Chemistry and Physics* R C Mellors Edit. New York, McGraw Hill Book Co 1957
534 Ratnoff O D *Hereditary Defects in Clotting Mechanisms* in *Ad vances in Internal Medicine* William Dock and I Snapper Editors Chicago The Year Book Publishers 9 107 1958
535 Ratnoff O D Hageman Trait, *Thromb et Diath Haem* (in press)
536 Ratnoff O D Unpublished Observations
537 Ratnoff O D and Colopy J E Familial hemorrhagic trait associated with deficiency of clot promoting fraction of plasma, *J Clin Invest 34* 602 1955
538 Ratnoff O D Colopy J E and Pritchard, J A The blood-clotting mechanism during normal parturition *J Lab & Clin Med 44* 408 1954
539 Ratnoff O D and Conley C L. Studies on afibrinogenemia II The defibrinating effect on dog blood of intravenous injection of thromboplastic material *Bull Johns Hopkins Hosp 88* 414 1950
540 Ratnoff O D Conley C L. and Berthrong, M The differentiation between extrahepatic and intrahepatic obstruction of the portal cir culation A clinical study of the Banti syndrome" *Bull Johns Hopkins Hosp 87* 305 1950
540a. Ratnoff O D and Donaldson V H Unpublished observations
540b Ratnoff O D and Donaldson V H Physiologic and pathologic effects of increased fibrinolytic activity in humans *Am J Cardiol* in press
541 Ratnoff O D and Holland T R Coagulation components in normal and abnormal pregnancies *Ann New York Acad Sc 75* 626 1959
542. Ratnoff O D and Margolius A Jr On epidemiology of hemophilia and Christmas disease *New Eng J Med 256* 845 1957
543 Ratnoff O D and Margolius A Jr *Hageman Factor and Hageman Trait* in *Hemophilia and Hemophilioid Diseases* Brinkhous K. M edit. Chapel Hill, U of N Carolina Press 1957
544 Ratnoff O D and Menzie C A new method for the determination of fibrinogen in small samples of plasma, *J Lab & Clin Med 37* 316 1951

514 Quick A J The anticoagulants effective *in vivo* with special reference to heparin and dicumarol, *Physiol Rev 24* 297 1944
515 Quick A J Studies on enigma of hemostatic dysfunction of hemophilia *Am J Med Sc 214* 272 1947
516 Quick A J Management of hemophilia in general practice *J A M A 145* 4 1951
517 Quick, A J *Hemorrhagic Diseases* Philadelphia Lea & Febiger 1957
518 Quick A J and Favre Gilly J E The prothrombin consumption test its clinical and theoretic implications *Blood 4* 1281 1949
519 Quick A J and Grossman A M The nature of the hemorrhagic disease of the newborn Delayed restoration of the prothrombin level *Am J Med Sc 199* 1 1940
520 Quick A J and Hussey C V Hemophilia Clinical and laboratory observations relative to diagnosis and inheritance *Am J Med Sc 223* 401 1952
521 Quick A J and Hussey C V Hemophilia B (PTC deficiency or Christmas disease) *A M A Arch Int Med 103* 762 1959
522 Quick A J Pisciotta A V and Hussey C V Congenital hypoprothrombinemic states *A.M.A Arch Int Med 95* 2 1955
523 Quick A J, Stanley Brown M and Bancroft F W A study of the coagulation defect in hemophilia and in jaundice *Am J Med Sc 190* 501 1935
524 Rabinovich S I The long term results of splenectomy in Werlhof's Disease *Problems of Hematology and Blood Transfusions 2* 100 1957
524a Rabinowitz, Y and Dameshek, W Systemic lupus erythematosus after idiopathic" thrombocytopenic purpura A review A study of systemic lupus erythematosus occurring after 78 splenectomies for "idiopathic" thrombocytopenic purpura with a review of the pertinent literature *Ann Int Med 52* 1 1960
525 Ralli E P and Sherry S Adult scurvy and the metabolism of Vitamin C *Medicine 20* 251 1942
526 Ramot B Angelopoulos B and Singer K Plasma thromboplastin antecedent deficiency *A M.A Arch Int Med 95* 705 1955
527 Rapaport S I and Chapman C C Coexistent hypercoagulability and acute hypofibrinogenemia in a patient with prostatic carcinoma *Am J Med 27* 144 1959
528 Rath C E Maillard J A and Schreiner G E Bleeding tendency in uremia *New Eng J Med 257* 808 1957
529 Ratnoff O D Studies on a proteolytic enzyme in human plasma IV The rate of lysis of plasma clots in normal and diseased individuals with particular reference to hepatic disease *Bull Johns Hopkins Hosp 84* 29 1949

562 Roos J vanArkel C Verloop M C and Jordan F L A "new" family with Stuart Prower deficiency *Thrombosis et Diathesis Haem.* 3 59 1959

563 Rose B Kovaks L Hanson S Richter M Gordon J Gyenes L and Sehon A H Macroglobulinemia A study of the serum proteins in four cases *Tr A Am Physicians* 69 139 1956

564 Rosenthal M C and Sanders M Plasma thromboplastin component deficiency studies on its inheritance and therapy *Am J Med* 16 153 1954

565 Rosenthal, N The blood picture in purpura *J Lab & Clin Med* 13 303 1928

566 Rosenthal, R L Properties of plasma thromboplastin antecedent (PTA) in relation to blood coagulation *J Lab & Clin Med* 45 123 1955

567 Rosenthal R L *The Present Status of Plasma Thromboplastin Antecedent (PTA) Deficiency* in *Hemophilia and Hemophilioid Diseases* K Brinkhous Edit Chapel Hill U of N Carolina Press 1957

568 Rosenthal R L Dreskin O H and Rosenthal N New hemophilia like disease caused by deficiency of third plasma thromboplastin factor *Proc Soc Exper Biol & Med* 82 171 1953

569 Roskam J Purpuras hémorragiques et thrombopénie (Étude expérimentale) Pathogénie du syndrome hémogénique engendré par l administration de sérum antiplaquettes *Le Sang* 8 129 1934

570 Rothman S *Physiology & Biochemistry of the Skin*, Chicago U of Chicago Press 1954

571 Rukavina J G Block W D Jackson C E Falls H F Carey J H and Curtis A C Primary systemic amyloidosis A review and an experimental genetic and clinical study of 29 cases with particular emphasis on the familial form *Medicine* 35 239 1956

572 Rukavina J G Dickison G and Curtis A C The simultaneous occurrence of urticaria pigmentosa and primary systemic amyloidosis Report of a case with autopsy findings *J Invest Dermat* 28 243 1957

573 Scanlon G H Brinkhous K M Warner E D Smith H P and Flynn J E Plasma prothrombin and the bleeding tendency with special reference to jaundiced patients and Vitamin K therapy *J A M A* 112 1898 1939

573a Scarborough H and Shuster S Corticosteroid purpura *Lancet* 1 93 1960

574 Schneider C L "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of end results during placenta abruptio *Surg Gynec & Obst* 92 27 1951

575 Schneider C L *Mechanisms of Production of Acute Fibrinogen De*

544a Ratnoff O D and Nebehay W To be published

545 Ratnoff O D Pritchard J A and Colopy J E Hemorrhagic states during pregnancy *New Eng J Med 254* 63 97 1955

545a Ratnoff O D Rasch C A and Griggs R C To be published

546 Ratnoff O D and Rosenblum J M Role of Hageman fatcor in the initiation of clotting by glass *Am J Med 25* 160 1958

546a Ratnoff O D Weisman R Jr and Stavitsky A B Unpublished Observations

547 Reed C S H and Firkin B G Autoerythrocytic sensitization with a circulating fibrinolytic factor *Australasian Ann Med 6* 58 1957

548 Rees H M and Ecker E E An improved method for counting blood platelets *J.A M.A 80* 621 1923

549 Rehbein A Jaretzki A III and Habif D V The response of dicumarol induced hypoprothrombinemia to Vitamin K, *Ann Surg 135* 454 1952

550 Reinhold J D L Neumark E Lightwood R and Carter C O Familial hypoplastic anemia with congenital abnormalities (Fanconi s syndrome) *Blood* 7 915 1952

551 Reisner E H Jr and Keating R P Survival of labeled platelets in X irradiated rabbits *Proc Soc Exper Biol & Med 96* 112 1957

552 Rendu M Epistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux *Bull et Mem Soc Med Hop de Paris 13* 731 1896

553 Revol L Favre Gilly J and Ollagnier C La maladie de Willebrand (thrombopathic constitutionelle ou pseudo hemophilie) *Rev d hemat 5* 24 1950

554 Risak E Die fibrinopenie *Ztschr klin Med 128* 605 1935

555 Roberts M H and Smith M H Thrombopenic purpura Report of four cases in one family *A M A J Dis Child. 79* 820 1950

556 Robertson M G and Schroder J S Pseudoxanthoma elasticum A systemic disorder *Am J Med 27* 433 1959

557 Robson H N Idiopathic thrombocytopenic purpura *Quart J Med n s 18* 279 1949

558 Robson H N Medical aspects of splenectomy *Edinburgh M J 56* 381 1949

559 Robson H N and Walker C H M Congenital and neonatal thrombocytopenic purpura *Arch Dis Childhood 26* 175 1951

560 Rodes C B Cavernous hemangiomas of the lung with secondary polycythemia *J A M A 110* 1914 1938

561 Rodman N F Jr Barrow E M and Graham J B Diagnosis and control of the hemophilioid states with the partial thromboplastin time (PTT) test, *Am J Clin Path 29* 525 1958

562 Roos J vanArkel C Verloop M C and Jordan F L A "new" family with Stuart Prower deficiency *Thrombosis et Diathesis Haem* 3 59 1959
563 Rose B Kovaks L Hanson S Richter M Gordon J Gyenes L and Sehon, A H Macroglobulinemia A study of the serum proteins in four cases *Tr A Am Physicians* 69 139 1956
564 Rosenthal M C and Sanders M Plasma thromboplastin component deficiency studies on its inheritance and therapy *Am J Med* *16* 153 1954
✓ 565 Rosenthal, N The blood picture in purpura *J Lab & Clin Med* *13* 303 1928
566 Rosenthal, R L Properties of plasma thromboplastin antecedent (PTA) in relation to blood coagulation *J Lab & Clin Med* *45* 123 1955
567 Rosenthal R L *The Present Status of Plasma Thromboplastin Antecedent (PTA) Deficiency in Hemophilia and Hemophilioid Diseases* K. Brinkhous Edit. Chapel Hill U of N Carolina Press 1957
568 Rosenthal, R L Dreskin O H and Rosenthal, N New hemophilia like disease caused by deficiency of third plasma thromboplastin factor *Proc Soc Exper Biol & Med* *82* 171 1953
569 Roskam J Purpuras hémorragiques et thrombopénie (Étude expérimentale) Pathogénie du syndrome hémogénique engendré par l'administration de sérum antiplaquettes *Le Sang* *8* 129 1934
570 Rothman S *Physiology & Biochemistry of the Skin* Chicago U of Chicago Press 1954
571 Rukavina J G Block W D Jackson C E Falls H F Carey J H and Curtis A C Primary systemic amyloidosis A review and an experimental genetic and clinical study of 29 cases with particular emphasis on the familial form *Medicine* *35* 239 1956
572 Rukavina J G Dickson G and Curtis A. C The simultaneous occurrence of urticaria pigmentosa and primary systemic amyloidosis Report of a case with autopsy findings *J Invest Dermat* *28* 243 1957
✓ 573 Scanlon G H Brinkhous K. M Warner E D Smith H P and Flynn J E Plasma prothrombin and the bleeding tendency with special reference to jaundiced patients and Vitamin K therapy *J.A M A* *112* 1898 1939
573a Scarborough H and Shuster S Corticosteroid purpura, *Lancet* *1* 93 1960
574 Schneider C L "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of end results during placenta abruptio *Surg Gynec & Obst* 92 27 1951
575 Schneider C L *Mechanisms of Production of Acute Fibrinogen De*

ficiencies in *Progress in Hematology* L M Tocantins edit. New York, Grune and Stratton 1956
576 Schulman I and Smith C H Hemorrhagic disease in infant due to deficiency of previously undescribed clotting factor *Blood* 7 794 1952
577 Schulman I Smith, C H Erlandson M Fort E and Lee R E Vascular hemophilia A familial hemorrhagic disease in males and females characterized by combined antihemophilic globulin deficiency and vascular abnormality *Ped* 18 347 1956
578 Schuster N H Familial hemorrhagic telangiectasia associated with multiple aneurysms of the splenic artery *J Path & Bact* 44 29 1937
579 Scott E V Z Matthews W F Butterworth, C E Jr and From meyer W B Jr Abnormal plasma proteolytic activity Diagnosis and treatment, *Surg Gynec & Obst* 99 679 1954
580 Scott, J L Cartwright G E and Wintrobe M M Acquired aplastic anemia An analysis of 39 cases and review of the pertinent literature *Medicine* 38 119 1959
581 Scott, R. Jr and Crosby W H Changes in the coagulation mechanism following wounding and resuscitation with stored blood A study of battle casualties in Korea, *Blood* 9 609 1954
582 Seegers W H The influence of certain drugs on blood coagulation and related phenomena *Pharmacol Rev* 3 278 1951
583 Seegers W H, McClaughry R I and Fahey J L Some properties of purified prothrombin and its activation with sodium citrate *Blood* 5 421 1950
584 Seegers W H and Smith H P Factors which influence activity of purified thrombin *Am J Physiol* 137 348 1942
585 Seibert R H Margolius A Jr and Ratnoff O D Observations on hemophilia parahemophilia and coexistent hemophilia and para hemophilia *J Lab & Clin Med* 52 449 1958
586 Seiden G F and Wurzel H A Idiopathic benign hyperglobulinemic purpura *New Eng J Med* 255 170 1956
587 Selling L and Osgood E The action of benzol Roentgen rays and radioactive substances on the blood and blood forming tissues in *Handbook of Hematology* H Downey edit New York, P B Hoeber Inc 4 2693 1938
588 Shaffer B Copelan H W and Beerman H Pseudoxanthoma Elasticum A cutaneous manifestation of a systemic disease Report of a case of Paget s disease and a case of calcinosis with arteriosclerosis as manifestations of this syndrome A M A *Arch Derm* 76 622 1957
589 Shafrir E and de Vries A. Studies on the clot promoting activity of glass *J Clin Invest* 35 1183 1956
590 Sharp A A Howie B Biggs R and Methuen, D R Defibrination

syndrome in pregnancy Value of various diagnostic tests *Lancet* 2 1309 1958
591 Shaw S and Oliver R A. M Congenital hypoplastic thrombocytopenia with skeletal deformities in siblings *Blood 14* 374 1959
592. Sherry S Fletcher A. P and Alkjaersig N Fibrinolysis and fibrinolytic activity in man *Physiol Rev* 39 343 1959
593 Sherry S and Troll, W Action of thrombin on synthetic substrates *J Biol. Chem* 208 95 1954
594 Shettles L. B Delfs E. and Hellman L. M Factors influencing plasma prothrombin in the newborn infant. II Antepartum & neonatal ingestion of Vitamin K concentrate *Bull Johns Hopkins Hosp 65* 419 1939
595 Shulman, N R Immunoreactions involving platelets *J Exper Med 107* 665 697 711 1958
596 Shulman, S Fibrin serum factor *Nature 171* 606 1953
597 Shulman S The size and shape of bovine fibrinogen Studies of sedimentation diffusion and viscosity J.A.C.S 75 5846 1953
598 Siegel, B M., Friedman, I A. and Schwartz, S O Hemorrhagic disease in osteogenesis imperfecta. Study of platelet functional defect, *Am J Med* 22 315 1957
599 Singer K. Thrombotic thrombocytopenic purpura *Advances Int Med.* 6 195 1954.
600 Singer K. Motulsky A. G and Shanberge J N Thrombotic thrombocytopenic purpura II Studies on the hemolytic syndrome in this disease *Blood* 5 434 1950
601 Singer K. and Ramot, B Pseudohemophilia type B Hereditary hemorrhagic diathesis characterized by prolonged bleeding time and decrease in antihemophilic factor A.M.A *Arch Int Med.* 97 715 1956
602. Singer K. and Wolfson, W Q Hereditary hemorrhagic telangiectasia. An analysis of capillary heredopathies *New Eng J Med 230* 637 1944
603 Sise H S Lavelle S M Adamis D and Becker R Relation of hemorrhage and thrombosis to prothrombin during treatment with coumarin type anticoagulants *New Eng J Med* 259 266 1958
604 Sise H S Lavelle S M and Becker R. A method for assay of Stuart Factor *Proc Soc Exper Biol & Med 96* 662 1957
605 Sjoerdsma, A Serotonin, *New Eng J Med 261* 231 1959
606 Skinner J B Serum hepatitis Occurrence following the use of human fibrinogen, *Missouri Med* 54 740 1957
607 Skold E On haemophilia in Sweden and its treatment by blood transfusion *Acta Med Scand Suppl 150* 1 1944
608 Smiley R. K. and Wintrobe M M Fatal aplastic anemia following chloramphenicol (Chloromycetin) administration, *J.A M.A. 149* 914 1952

609 Smith C H Erlandson M Schulman I and Stern G Hazard of severe infections in splenectomized infants and children *A M.A. J Dis Childhood* 92 507 1956
610 Smith H P Warner E D and Brinkhous K M Prothrombin deficiency and bleeding tendency in liver disease (chloroform intoxication) *J Exper Med* 66 801 1937
611 Smith H P Warner E D Brinkhous K M and Seegers W H Bleeding tendency and prothrombin deficiency in bile fistula dogs Effect of feeding bile and Vitamin K *J Exper Med* 67 911 1938
612 Soffer L J and Bader R Corticotropin and cortisone in acute disseminated lupus erythematosus Results of long term use *J.A M.A.* 149 1002 1952
613 Soulier J P Étude génétique des syndromes hémorrhagiques *Sang* 25 355 1954
614 Soulier J P and Alagille D Allongement du temps de saignement associé a un déficit en facteur anti hémophilique A *Rev franç étud clin et biol* 1 187, 1956
615 Soulier, J P Alagille D and Larrieu M J Physiopathologie des hemorragies an cours des hyperplaquettoses Etude de'l hémostase chez 27 malades *Le Sang* 28 277 1957
616 Soulier J P and Larrieu M J Differentiation of hemophilia into two groups a study of 33 cases *New Eng J Med* 249 547 1953
617 Soulier J P and Larrieu M J Syndrome de Willebrand Jürgens et thrombopathies Étude de 65 cas Essai de classification *Rev d'hémat* 9 77 1954
618 Soulier J P and Larrieu M J Déficit en 3ème facteur prothromboplastique plasmatique Rapports entre le PTA et le facteur Hageman *Thrombosis et Diath Haem* 2 1 1958
619 Soulier, J P Larrieu M J and Wartelle O La thromboplastinoformation dans les affections plaquettaires Étude de 34 cas a l aide du test de Biggs et Douglas *Acta haemat* 14 160, 1955
620 Soulier J P Mathey J LeBolloch A. G Daumet, P and Fayet H Syndromes hemorrhagiques mortels avec incoagulabilité totale par défibrination et avec fibrinolyse *Rev d'hemat* 7 30 1952
621 Soulier J P Wartelle O and Ménaché D Hageman factor and PTA deficiency the role of contact of blood with glass *Brit J Haemat* 5 121 1959
622 Soumerai S and MacGillivray W F Thrombotic thrombocytopenic purpura Report of a case with a review of the pathogenesis of the disease *New Eng J Med* 255 585 1956
623 Spaet T Recent progress in the study of hemophilia, *Stanford M Bull* 13 24 1955
624 Spaet, T H and Kropatkin, M Studies on "prothrombin derivatives" in Vitamin K deficiency *A M.A Arch Int Med* 102 558 1958

625 Spaet, T H and Garner E S Resistance to transfusion in hemophilia and deuterohemophilia, *Stanford M Bull 13* 188 1955
626 Spaet, T H Kinsell, B Behring H M and Aggeler P M Atypical blood clotting patterns in hemophilia *Stanford M Bull 11* 118 1953
627 Spurling, C L. and Sacks M S Inherited hemorrhagic disorder with antihemophilic globulin deficiency and prolonged bleeding time *New Eng J Med. 261* 311 1959
628 Stefanini, M and Gendel, B R Influence of fibrinolysin on the survival "in vivo" of various coagulation factors and favorable effect of cortisone in "fibrinolytic purpura," *Clin Res Proc 1* 5 1953
629 Stefanini, M Chatterjea, J B and Adelson, E Immunologic aspects of idiopathic thrombocytopenic purpura (I T.P) *J Clin Invest 31* 665 1952
630 Stefanini, M., Chatterjea J B Dameshek, W Zannos L and Santiago E P Studies on platelets II The effect of transfusion of platelet rich polycythemic blood on the platelets and hemostatic function in "idiopathic" and "secondary" thrombocytopenic purpura, *Blood 7* 53 1952
631 Stefanini, M and Crosby W H The one-stage prothrombin consumption test Clinical value in the identification of thromboplastin deficiency diseases *Blood 5* 964 1950
632 Stefanini, M and Dameshek W Idiopathic thrombocytopenic purpura A challenge *Lancet 2* 209 1953
✓ 633 Stefanini, M and Dameshek, W *The Hemorrhagic Disorders A Clinical and Therapeutic Approach* New York, Grune and Stratton, 1955
634 Stefanini, M Dameshek, W and Adelson E Platelets VII Shortened "platelet survival time" and development of platelet agglutinins following multiple platelet transfusions *Proc Soc Exper Biol & Med 80* 230 1952
635 Stefanini, M and Martino N B Use of prednisone in the management of some hemorrhagic states *New Eng J Med 254* 313 1956
636 Stefanini, M Mednicoff I B Salomon, L and Campbell E W Thrombocytopenia of replacement transfusion. A cause of surgical bleeding, *Clin Res Proc 2* 61 1954
637 Stefanini, M Piomelli, S Mele R. Ostroski, J T and Colpoys W P Acute vascular purpura following immunization with Asiatic-influenza vaccine *New Eng J Med 259* 9 1958
638 Stefanini, M and Rosenthal M C Hemorrhagic diathesis with ascorbic acid deficiency during administration of anterior pituitary corticotropic hormone (ACTH) *Proc Soc Exper Biol & Med 75* 806 1951
639 Stefanini, M Roy C A. Zannos L. and Dameshek, W Therapeutic

609 Smith C H Erlandson M Schulman I and Stern G Hazard of severe infections in splenectomized infants and children *A M A J Dis Childhood* 92 507 1956

610 Smith H P Warner E D and Brinkhous K M Prothrombin deficiency and bleeding tendency in liver disease (chloroform intoxication) *J Exper Med* 66 801 1937

611 Smith H P Warner E D Brinkhous K M and Seegers W H Bleeding tendency and prothrombin deficiency in bile fistula dogs Effect of feeding bile and Vitamin K *J Exper Med* 67 911 1938

612 Soffer L J and Bader R Corticotropin and cortisone in acute disseminated lupus erythematosus Results of long term use *J A M A* 149 1002 1952

613 Soulier J P Étude génétique des syndromes hémorrhagiques *Sang* 25 355 1954

614 Soulier J P and Alagille D Allongement du temps de saignement associé a un déficit en facteur anti hémophilique A *Rev franç étud clin et biol* 1 187 1956

615 Soulier J P Alagille D and Larrieu M J Physiopathologie des hémorragies au cours des hyperplaquettoses Etude de l hémostase chez 27 malades *Le Sang* 28 277 1957

616 Soulier J P and Larrieu M J Differentiation of hemophilia into two groups a study of 33 cases *New Eng J Med* 249 547 1953

617 Soulier J P and Larrieu M J Syndrome de Willebrand Jurgens et thrombopathies Étude de 65 cas Essai de classification *Rev d hémat* 9 77 1954

618 Soulier J P and Larrieu M J Déficit en 3ème facteur prothromboplastique plasmatique Rapports entre le PTA et le facteur Hageman *Thrombosis et Diath Haem* 2 1 1958

619 Soulier J P Larrieu M J and Wartelle O La thromboplastinoformation dans les affections plaquettaires Étude de 34 cas a l aide du test de Biggs et Douglas *Acta haemat* 14 160 1955

620 Soulier J P Mathey J LeBolloch A G Daumet P and Fayet H Syndromes hemorrhagiques mortels avec incoagulabilité totale par défibrination et avec fibrinolyse *Rev d'hémat* 7 30 1952

621 Soulier J P Wartelle O and Ménaché D Hageman factor and PTA deficiency the role of contact of blood with glass *Brit J Haemat* 5 121 1959

622 Soumerai S and MacGillivray W F Thrombotic thrombocytopenic purpura Report of a case with a review of the pathogenesis of the disease *New Eng J Med* 255 585 1956

623 Spaet T Recent progress in the study of hemophilia *Stanford M Bull* 13 24 1955

624 Spaet T H and Kropatkin M Studies on "prothrombin derivatives" in Vitamin K deficiency *A M A Arch Int Med* 102 558 1958

656 Telfer T P Denson K W and Wright, D R New coagulation defect *Brit J Haemat* 2 308 1956
657 Thiers H Favre Gilly J Fayolle J Colomb D Chassard A. and Thouverez, J P Purpura hémorrhagique mortel avec héparin émie au cours d une lupo-érythémato-viscérite *Lyon med* 90 961 1958
658 Thomas H B Some orthopedic findings in 98 cases of hemophilia *J Bone & Joint Surg* 18 140 1936
659 Thomas L. Studies on the intravascular thromboplastic effect of tissue suspensions in mice II A factor in normal rabbit serum which inhibits the thromboplastic effect of the sedimentable tissue com ponent, *Bull Johns Hopkins Hosp* 81 26 1947
660 Tocantins L M The mammalian blood platelet in health and dis ease *Medicine* 17 155 1938
661 Tocantins L M edit *The Coagulation of Blood Methods of Study* New York Grune and Stratton 1955
662 Tocantins L M Treatment of hemophilia *Blood* 11 89 1956
663 Tocantins L M and Carroll, R T Separation and assay of a lipid antithromboplastin from human brain *Tr of Second Conference on Blood Clotting and Allied Problems* New York, Josiah Macy Jr Foundation 1949
664 Tocantins L M Carroll, R T and Holburn R H Clot accelerating effect of dilution on blood and plasma relation to mechanism of coagulation of normal and hemophilic blood *Blood* 6 720 1951
665 Trobaugh F E Jr Markowitz, M Davidson C S and Crowley W F An acute febrile illness characterized by thrombocytopenic purpura hemolytic anemia and generalized platelet thrombi *Arch Path* 41 327 1946
666 Troland C E and Lee F C Thrombocytopen a substance in the extract from the spleen of patients with idiopathic thrombocyto penic purpura that reduces the number of blood platelets *J.A M.A* 111 221 1938
667 Troup S B and Reed C F Platelet thromboplastic factor Its chemical nature *in vitro* activity and the identification of similar thromboplastic substances in red blood cells *J Clin Invest* 37 937 1958
668 Tuller M A Amniotic fluid embolism afibrinogenemia and dissemi nated fibrin thrombosis Case report and review of the literature *Am J Obst & Gynec* 73 273 1957
669 Tullis J L Platelet antibody tests in the diagnosis of purpura *New Eng J Med* 249 591 1953
670 Tullis J L Identification and significance of platelet antibodies *New Eng J Med* 255 541 1956
671 Tumulty P A and Harvey A. M The clinical course of disseminated

effect of pituitary adrenocorticotropic hormone (ACTH) in a case of Henoch Schonlein vascular (anaphylactoid) purpura, *J.A.M.A* *144* 1372 1950
640 Steiner, P E and Lushbaugh, C C Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexpected deaths in obstetrics *J.A M.A* *117* 1245 1941
641 Steinhardt I D and Jonas A F Coexistence of intussusception and Henoch s purpura *New Eng J Med* *257* 553 1957
642 Steinhardt M J and Fisher G S Essential cryoglobulinemia, *Ann Int Med* *43* 848 1955
643 Stoesser, A V and Lockwood, W W Varicella complicated with acute thrombocytopenic purpura and gangrene, *J Pediat* *12* 641, 1938
644 Stouffer J G and Ashworth C T Hypofibrinogenemia and the placenta, *Am J Obst & Gynec* *75* 407 1958
645 Strangway W E and Strangway A K Ascorbic acid deficiency in the African disease Onyalai *Arch Int Med* *83* 372 1949
646 Strauss, W G Purpura hyperglobulinemia of Waldenstrom Report of a case and review of the literature *New Eng J Med* *260* 857 1959
647 Streuli F On the purification and conversion of human prothrombin *Thrombosis et Diath Haem* *3* 194 1959
648 Stuart A E and MacGregor Robertson G Thrombotic thrombo cytopenic purpura A hyperergic microangiopathy *Lancet* *1* 475, 1956
649 Sykes E M Seegers W H and Ware A. G Effect of acute liver damage on Ac globulin activity of plasma *Proc Soc Exper Biol & Med* *67* 506 1948
650 Symmers W St C Thrombotic microangiopathy Histologic diag nosis during life *Lancet* *1* 592 1956
651 Symmers W St C Amyloidosis Five cases of primary generalized amyloidosis and some other unusual cases *J Clin. Path* *9* 212 1956
652 Tagnon H J Levenson S M Davidson C S and Taylor F H L The occurrence of fibrinolysis in shock with observations on the prothrombin time and the plasma fibrinogen during hemorrhagic shock, *Am J Med Sc* *211* 88 1946
653 Tagnon H J Whitmore W F, Jr Schulman P and Kravitz, S C The significance of fibrinolysis occurring in patients with metastatic cancer of the prostate *Cancer* *6* 63 1953
654 Tattersall R N and Seville R Senile purpura *Quart J Med n s* *19* 151 1950
655 Taylor K. B and Wright F W Purpura gangrenosa *Lancet* *2* 284 1956

proteinemia and their practical value for diagnosis *Nord Med* *20* 2288 1943

688 Waldenstrom J Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—a new syndrome? *Acta med scand* *117* 216 1944

689 *Waldenstrom J Three new cases of purpura hyperglobulinemica* A study in long lasting benign increase in serum globulin *Acta med scand Suppl 266* 931 1952

690 Waldenstrom J Abnormal proteins in myeloma *Advances Int Med* *5* 398 1952

691 Waldenstrom J Macroglobulinaemia, *Acta haemat 20* 33 1958

692 Wang C I and Bossak E T *Hemorrhagic Manifestations in Idiopathic Sprue* A report of 25 cases and a review of the literature in *The Malabsorption Syndrome* D Adlersberg Edit. New York, Grune and Stratton 1957

693 Ware A G Fahey J L and Seegers W H Platelet extracts fibrin formation and interaction of purified prothrombin and thromboplastin *Am J Physiol 154 140 1948*

694 Ware A G and Seegers W H Serum Ac globulin formation from plasma Ac-globulin role in blood coagulation partial purification properties and quantitative determinations *Am J Physiol 152 567* 1948

695 Warner E D Brinkhous K M and Smith, H P A quantitative study of blood clotting prothrombin fluctuations under experimental conditions *Am J Physiol 114* 667 1936

696 Warner E D Brinkhous K M and Smith H P Bleeding tendency of obstructive jaundice Prothrombin deficiency and dietary factors *Proc Soc Exper Biol & Med 37 628 1938*

697 Watson Williams E J Macpherson A I S and Davidson S The treatment of idiopathic thrombocytopenic purpura *Lancet* 2 221 1958

698 Weber F Parkes A case of multiple hereditary developmental angiomata (telangiectases) of the skin and mucous membranes associated with recurring haemorrhages *Lancet 2* 160 1907

698a Wedgwood R J P Anaphylactoid purpura in *Textbook of Pediatrics* seventh edition W E Nelson edit Philadelphia W B Saunders Co 1959

699 Wedgwood R J P and Janeway C A Serum complement in children with "collagen diseases" *Ped 11* 569 1953

700 Wedgwood R J P and Klaus M H Anaphylactoid purpura (Schonlein Henoch syndrome) A long term follow up study with special reference to renal involvement *Ped 16* 196 1955

701 Weil Malherbe H and Bone A D *Blood platelets as carriers of* adrenaline and noradrenaline *Nature 174* 557 1954

702 Weiner A E and Reid D E Pathogenesis of amniotic fluid em

lupus erythematosus An evaluation of Oslers contribution *Bull Johns Hopkins Hosp* 85 47 1949
672 Tunbridge, R E Tattersall R N Hall D A. Astbury W J and Reed R The fibrous structure of normal and abnormal human skin *Clin Sc 11* 315 1952
673 VanCreveld S Congenital idiopathic hypoprothrombinemia *Acta Paediat Suppl 100* 245 1954
674 Vandenbroucke J and Verstraete M Thrombocytopenia due to platelet agglutinins in the newborn *Lancet 1* 593 1955
675 Vandenbroucke, J Verstraete M and Verwilghen R L afibrinogéné mie congénitale Présentation d un nouveau cas et revue de la littérature *Acta Haemat* 12 87 1954
676 Verstraete M and Vandenbroucke J Occurrence and mode of action of endogenous circulating anticoagulants *J Lab & Clin Med 48* 673 1956
677 Vilter R W *Ascorbic Acid Effects of Deficiency in Human Beings in The Vitamins Chemistry Physiology Pathology* W H Sebrell Jr and R S Harris edits New York Academic Press 1954
678 Voigt A E and Frick P G Macroglobulinemia of Waldenstrom A review of the literature and presentation of a case *Ann Int Med 44* 419 1956
679 Volpé R Bruce Robertson A Fletcher A A and Charles W B Essential cryoglobulinaemia Review of the literature and report of a case treated with ACTH and cortisone *Am J Med 20* 533 1956
680 Volwiler W Goldsworthy, P D, MacMartin M P Wood P A *Mackay I R and Fremont Smith K Biosynthetic determination with radioactive sulfur of turnover rates of various plasma proteins in normal and cirrhotic man J Clin Invest 34* 1126 1955
681 von Kaulla K N and Swan H Clotting deviations in men during cardiac by pass Fibrinolysis and circulating anticoagulant *J Thoracic Surg 36* 519 1958
682 von Willebrand E A Über hereditare pseudohamophilie *Acta Med Scand 76* 521 1931
683 von Willebrand W and Jurgens R Über eine neue Bluterkrankheit die konstitutionelle Thrombopathie *Klin Wchnschr* 12 414, 1933
684 Vroman L Surface contact and thromboplastin formation Thesis University of Utrecht 1958
685 Waaler B A Contact activation in the intrinsic blood clotting system Studies on a plasma product formed on contact with glass and similar surfaces *Scandinav J Clin & Lab Invest 11* Suppl 37 1 1959
686 Waddell W W and Guerry D III The role of vitamin K in the etiology prevention and treatment of hemorrhage in the newborn infant *J Pediat 15* 802 1939
687 Waldenstrom J Clinical methods for the determination of hyper

Negro familv manifested by thrombocytopenia eczema bloody diarrhea recurrent infection anemia and epistaxis *A M.A J Dis Childhood* 93 74 1957

720 Woodrow J C and Cope S Haemorrhagic thrombocythaemia treated with radioactive phosphorus *Brit M J* 2 1069 1955

721 Wooley E J S Familial idiopathic thrombocytopenic purpura *Brit M J 1* 440 1956

722 Wosilait W D and Nason A Pyridine nucleotide menadione reductase from Escherichia coli *J Biol Chem* 208 785 1954

722a. Wright, D O Reppert L. B and Cuttino J T Purpuric manifestations of heat stroke Studies of prothrombin and platelets in 12 cases *Arch Int Med* 77 27 1946

723 Wright J H and Minot G R The viscous metamorphosis of the blood platelets *J Exper Med 26* 395 1917

724 Zinkham W H An *in vitro* abnormality of glutathione metabolism in erythrocytes from normal newborns mechanism and clinical significance *Ped* 23 18 1959

725 Zinneman H H Dysproteinemia *Postgrad Med* 23 550 1958

726 Zlotnick A. Macroglobulinemia of Waldenstrom, *Am J Med 24* 461 1958

727 Zubrod C G Hilbish T F., Fahey J L Dutcher T F Fox, F A. and Osserman E F Waldenstrom s macroglobulinemia Clinical pathologic conference at the National Institutes of Health *Ann Int Med* 50 1010 1959

728 Zucker M B Friedman B K and Rapport, M M Identification and quantitative determinations of serotonin (5 Hydroxytryptamine) in blood platelets *Proc Soc Exper Biol & Med* 85 282 1954

729 Zucker M B Siegel, M Cliffton E E Bellville J W Howland, W S and Grossi C E Generalized excessive oozing in patients undergoing major surgery and receiving multiple blood transfusions *J Lab & Clin Med 50* 849 1957

730 Allison A C Acute haemolytic anemia with distortion and fragmentation of erythrocytes in children *Brit J Haemat 3* 1 1957

731 Shumway C N Jr and Miller G An unusual syndrome of hemolytic anemia thrombocytopenic purpura and renal disease *Blood,* 12 1045 1957

bolism III Coagulant activity of amniotic fluid *New Eng J Med* *243* 597 1950

703 Weiner A E Reid D E and Roby C C Incoagulable blood in severe premature separation of the placenta method of management *Am J Obst & Gynec 66* 475 1953

704 Weiner A E Reid D E Roby C C and Diamond L K Coagulation defects with intrauterine death from Rh isosensitization *Am J Obst & Gynec 60* 1015 1950

705 Weisberger A S and Surhland L G Massive corticosteroid therapy in the management of resistant thrombocytopenic purpura *Am J Med Sc 236* 425 1958

706 Weissman J and Tagnon H J Syndrome of hemangioma and thrombocytopenic purpura in infants *A M A Arch Int Med 92* 523 1953

707 Welch, R G Thrombocytopenic purpura and chickenpox *Arch Dis Childhood 31* 38 1956

708 Whipple G H and Hurwitz S H Fibrinogen of the blood as influenced by the liver necrosis of chloroform poisoning *J Exper Med 13* 136 1911

709 White D W Home Care of the Hemophilic Child New York, National Hemophilic Foundation 1958

710 White S G Lagen J B Aggeler P M and Geyer R P Effect of soybean phosphatide on blood coagulation defect following total body X irradiation in the dog *Proc Soc Exper Biol & Med 83* 384 1953

711 Wilde H and Hitzelberger A L Macroglobulinemia Clinical features and differential diagnosis *Blood 9* 875 1954

712 Wile S A and Sturgeon P Thrombotic thrombocytopenic purpura Review of the subject with a report of 3 cases in children *Ped 17* 882 1956

713 Williams J A Belko J S and Warren R Thrombocytogenesis in surgical patients *Circulation Res 3* 285 1955

714 Winkelmann R K Clinical and pathologic findings in the skin in anaphylactoid purpura (allergic angiitis) *Proc Staff Meet Mayo Clin 33* 277 1958

715 Wintrobe M M *Clinical Hematology* 4th Edition Philadelphia Lea and Febiger 1956

716 Wintrobe M M and Buell, M V Hyperproteinemia associated with multiple myeloma, *Bull Johns Hopkins Hosp 52* 156 1933

717 Witts L J Chronic leg ulcer in purpura haemorrhagica Report of two cases *Brit M J 2* 309 1942

718 Wolbach S B and Bessey O A. Tissue changes in vitamin deficiencies *Physiol Rev 22* 233 1942

719 Wolff J A and Bertucio M A sex linked genetic syndrome in a

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